Synthesis of New Paramagnetic Selenophenes

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Dedicated to Professor George Sosnovsky on the occasion of his 90th birthday

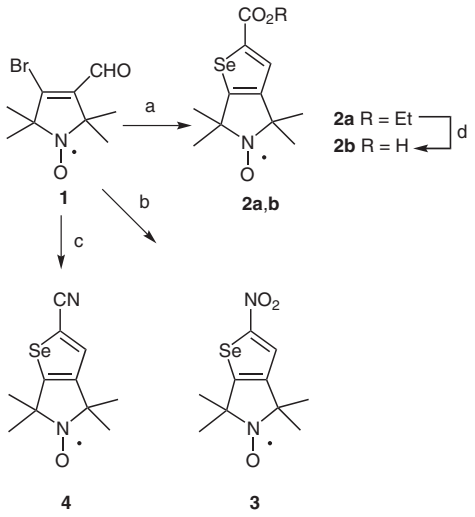
Abstract: Starting from 3-bromo-4-formyl- or 3-bromo-4-cyano-2,2,5,5,-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl radicals, 2-substituted and 2,3-disubstituted 5*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl radicals were synthesized. The 2-(bromomethyl)-substituted 5*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl derivative was a key intermediate in the synthesis of a thiol specific methanethiosulfonate spin label reagent, a paramagnetic, selenophene ring-containing amino acid, and a new quinazolin-4(3*H*)-one derivative.

Key words: amino acids, alkylations, free radicals, heterocycles, selenium

Interest in the use of organoselenium compounds, especially selenium-containing heterocyclic systems, as potential pharmaceuticals and building blocks for new materials has grown rapidly and there have been many publications in this area.[1–3]

Selenophenes have found many applications as analogues of thiophenes in drugs, such as selenosartans which have proven to be as active as sartans.[4] Compound D-501036, a novel selenophene derivative was found to be an effective cytotoxic agent with a broad spectrum of antitumor activity.[5] Selenophenes were reported to be used in the construction of organic-polymer-based field-effect transistors.[6] The above applications require new methods to be established for the synthesis[7] and derivatization of selenophenes.[8] Very recently a convenient, modified Fieselmann method[9] was reported for the synthesis of selenophenes.[10,11] From our laboratory, the thieno[2,3-*c*]pyrrol-5-yloxyl radical was reported 12 years ago[12] and we found it to be a useful synthon for the construction of a PARP-inhibitor[13] and a new unnatural α-amino acid.[14] We decided to synthesize the selenophene analogue because, as far as we know, no paramagnetic selenophenes have been synthesized. The wide range of applications of nitroxides such as spin labels,[15] spin traps,[16] co-oxidants,[17] or SOD-mimics[18] inspired us to synthesize nitroxides condensed with a new heterocycle; it was a challenge to obtain selenolo[2,3-*c*]pyrrol-5-yloxyl radicals. In this paper we report the synthesis of this new ring system and possible pathways for further modifications.

Treatment of compound **1** with freshly prepared sodium selenide[10] followed by treatment with ethyl chloroacetate and sodium ethoxide in aqueous *N*,*N*-dimethylformamide gave a mixture of ester **2a** (20%) and acid **2b** (40%) (method A). After chromatographic isolation compound **2b** was converted into **2a** by alkylation with iodoethane in the presence of DBU in acetonitrile (method B).[19] The treatment of compound **1** with sodium selenide and bromonitromethane under the same conditions as above with sodium hydroxide as the base furnished paramagnetic 2-nitroselenophene **3** in 38% yield, while treatment of **1** with sodium selenide and chloroacetonitrile and sodium hydroxide as the base gave compound **4** in 35% yield (Scheme 1).



Scheme 1 Reagents and conditions: (a) (i) Na_2Se (1.0 equiv), DMF–H_2O, 50 °C, 30 min, N_2, (ii) **1** (1.0 equiv), DMF, 50 °C, 30 min, (iii) $ClCH_2CO_2Et$ (1.0 equiv), DMF, 50 °C, 1 h, (iv) NaOEt (1.0 equiv), 30 min; 20% (**2a**), 40% (**2b**); (b) (i) Na_2Se (1.0 equiv), DMF–H_2O, 50 °C, 30 min, N_2, (ii) **1** (1.0 equiv), 50 °C, 30 min, (iii) $BrCH_2NO_2$ (1.0 equiv), DMF, 50 °C, 1 h, (iv) NaOH (1.0 equiv), H_2O, 50 °C, 30 min, 38%; (c) (i) Na_2Se (1.0 equiv), DMF–H_2O, 50 °C, 30 min, N_2, (ii) **1** (1.0 equiv), 30 min (iii) $ClCH_2CN$ (1.0 equiv), DMF, 50 °C, 1 h, (iv) NaOH (1.0 equiv), H_2O, 50 °C, 30 min, 35%; (d) EtI (1.0 equiv), DBU (1.0 equiv), MeCN, r.t., 12 h, 79%.

The structure of **2a** was proven by reducing the paramagnetic compound with iron/acetic acid[20] and the resulting diamagnetic compound showed a ^1H NMR signal δ = 7.64 and a ^{77}Se NMR signal in $CDCl_3$ at δ = 545 (^{77}Se signal of

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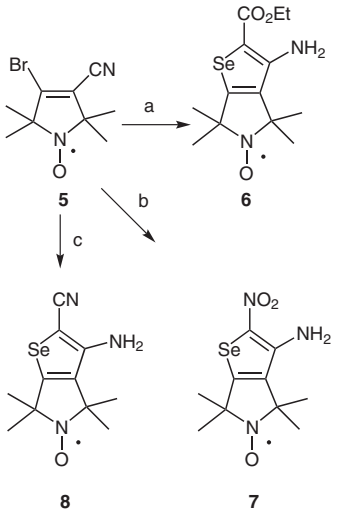
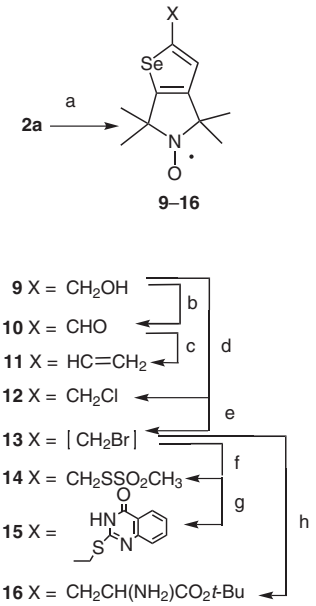
unsubstituted selenophene was found at δ = 542[21]) supported the selenophene ring formation.

The 2,3-disubstituted selenophene derivatives were available by starting with β-bromo-α,β-unsaturated nitrile **5**, sodium selenide treatment followed by addition of ethyl chloroacetate, bromonitromethane, or chloroacetonitrile and the corresponding base gave nitroxide annulated 3-amino-2-(ethoxycarbonyl)selenophene **6**, 3-amino-2-nitroselenophene **7**, and 3-amino-2-cyanoselenophene **8**, respectively (Scheme 2).



Scheme 2 *Reagents and conditions:* (a) (i) Na_2Se (1.0 equiv), DMF–H_2O, 50 °C, 30 min, N_2, (ii) **5** (1.0 equiv), DMF, 50 °C, 30 min, (iii) $ClCH_2CO_2Et$ (1.0 equiv), DMF, 50 °C, 1 h, (iv) DBU (1.0 equiv), 50 °C, 30 min, 16%; (b) (i) Na_2Se (1.0 equiv), DMF–H_2O, 50 °C, 30 min, N_2, (ii) **1** (1.0 equiv), DMF, 50 °C, 30 min (iii) $BrCH_2NO_2$ (1.0 equiv), DMF, 50 °C, 1 h, (iv) NaOH (1.0 equiv), H_2O, 50 °C, 30 min, 10%; (c) (i) Na_2Se (1.0 equiv), DMF–H_2O, 50 °C, 30 min, N_2, (ii) **1** (1.0 equiv), DMF, 50 °C, 30 min (iii) $ClCH_2CN$ (1.0 equiv), DMF, 50 °C, 1 h, (iv) NaOH (1.0 equiv), H_2O, 50 °C, 30 min, 12%.

We studied the possible reactions of 5*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl radicals. Reduction of compound **2a** with Red-Al in tetrahydrofuran yielded alcohol **9**, which was oxidized to aldehyde **10** with activated manganese(IV) oxide in chloroform. Compound **10** in a phase-transfer reaction with methyltriphenylphosphonium iodide in the presence of potassium carbonate in dioxane gave the 2-vinyl derivative **11**, which may be a useful co-polymerization building block. Alcohol **9** was converted into the corresponding isolable chloromethyl compound **12** by treatment of the mesylate with lithium chloride in acetone.[22] In an analogous procedure with lithium bromide, isolation of the bromomethyl compound failed. The bromomethyl derivative could be synthesized by treating the alcohol with carbon tetrabromide in dichloromethane in the presence of triphenylphosphine. Although the isolation of bromomethyl compound **13** in a pure form was not successful, the crude product could be used immediately in the next step. The reaction of the bromomethyl compound **13** with sodium methanethiosulfonate in aqueous acetone gave methanethiosulfonate **14** capable of SH-specific spin labeling.[23] Alkylation of 2-mercaptoquinazolin-4(3*H*)-one in *N*,*N*-dimethylformamide[24] with compound **13** in the presence of potassium carbonate yielded quinazolin-4(3*H*)-one derivative **15**. The treatment of *N*-(diphenylmethylene)glycine *tert*-butyl ester with compound **13** under phase-transfer conditions[25,26] followed by hydrolysis of the imine yielded selenophene-containing paramagnetic unnatural *rac*-amino acid **16** (Scheme 3).



Scheme 3 *Reagents and conditions:* (a) (i) Red-Al (1.25 equiv.), THF, 0 °C to r t., 30 min, N_2, and workup, (ii) PbO_2 (0.1 equiv), O_2, CH_2Cl_2, 15 min, 65%; (b) MnO_2 (10 equiv), $CHCl_3$, reflux, 1 h, 73%; (c) $MePh_3PI$ (1.0 equiv), K_2CO_3 (1.0 equiv), KOH (0.1 equiv), 18-crown-6 (cat.), dioxane, reflux, 48 h, 59%; (d) (i) MsCl (1.1 equiv), Et_3N (1.1 equiv), CH_2Cl_2, 0 °C to r.t., (ii) LiCl (2.0 equiv.), acetone, reflux, 40 min, 48%; (e) CBr_4 (1.33 equiv), Ph_3P (1.66 equiv), CH_2Cl_2, 0 °C, 30 min, 36%; (f) $NaSSO_2Me$ (2.0 equiv), acetone–H_2O, 50 °C, 45 min, 33%; (g) 2-mercaptoquinazolin-4(3*H*)-one (1.0 equiv), K_2CO_3 (1.0 equiv), DMF, reflux, 3 h, 42%; (h) (i) $Ph_2NCH_2CO_2t$-Bu (1.0 equiv), 10% aq NaOH, CH_2Cl_2, Bu_4NHSO_4 (0.5 equiv), r.t., 2 h, (ii) 5% aq H_2SO_4, EtOH, r.t. , 30 min, (iii) solid K_2CO_3 to pH = 8, H_2O, 46%.

In conclusion, we have extended the repertoire of the synthesis of heterocycle condensed pyrroline nitroxides. Selenolo[2,3-*c*]pyrrol-5-yloxyl rings were obtained by the reaction of 3-bromo-4-formyl- or 3-bromo-4-cyano-2,2,5,5,-tetramethyl-2,5-dihydro-1*H*-pyrrol-1-yloxyl radicals with sodium selenide and a nucleophile and electrophile center containing reagent. The 2-substituted selenophenes could be further converted into various paramagnetic selenophenes that are unique building blocks for the synthesis of drugs, paramagnetic amino acids, or spin label reagents. An investigation of the biological applications of the new selenophene derivatives is under way.

Melting points were determined with a Boetius micro melting point apparatus and are uncorrected. Elemental analyses (C, H, N, S) were performed on Fisons EA 1110 CHNS elemental analyzer. The

IR (Specord 85) spectra were in each case consistent with the assigned structure. Mass spectra were recorded on a Thermoquest Automass Multi and VG TRIO-2 instruments in the EI mode and ESI-TOF MS measurement was performed with a BioTOF II instrument (Bruker Daltonics, Billerica, MA). ^{1}H NMR spectra were recorded with Varian Unity INOVA 400 WB spectrometer; chemical shifts are referenced to TMS with 298 K probe in $CDCl_3$ soln.

ESR spectra were taken on Miniscope MS 200 in 10^{-4} M $CHCl_3$ soln and all monoradicals gave triplet line a_N = 14.4 G. Flash column chromatography was performed on Merck Kieselgel 60 (0.040–0.063 mm). Qualitative TLC was carried out on commercially available plates (20 × 20 × 0.02 cm) coated with Merck Kieselgel GF_{254}. Compounds **1**, **5**[12] were prepared according to published procedures and other reagents were purchased from Aldrich. Compound **2a** was reduced to its diamagnetic derivative for NMR study as published earlier.[20]

2-(Ethoxycarbonyl)-4,4,6,6-tetramethyl-5,6-dihydro-4*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl Radical (2a) and 2-Carboxy-4,4,6,6-tetramethyl-5,6-dihydro-4*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl Radical (2b) (Method A)

A suspension of freshly made Na_2Se (625 mg, 5.0 mmol) in DMF (10 mL) and H_2O (0.5 mL) was stirred under N_2 at 50 °C for 30 min. To this was added, in 1 portion, **1** (1.25 g, 5.0 mmol) in DMF (5 mL) and the mixture was stirred at 50 °C for 30 min. Ethyl chloroacetate (612 mg, 5.0 mmol) in DMF (2 mL) was added and the mixture was stirred at 50 °C for 1 h. NaOEt [5.0 mmol, made freshly from Na (115 mg) and EtOH (5 mL)] was added and the mixture was stirred at 50 °C for a further 30 min. The mixture was cooled, the solvents were evaporated off in vacuo, and the residue was partitioned between EtOAc (20 mL) and 5% aq H_2SO_4 (10 mL). The organic phase was separated, the aqueous phase was washed with EtOAc (20 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–Et_2O, 2:1 and $CHCl_3$–MeOH 9:1) to give **2a** (315 mg, 20%) as the first band and **2b** (574 mg, 40%) as the second band.

Ethyl Ester 2a

Pale yellow solid; mp 117–118 °C; R_f = 0.36 (hexane–Et_2O, 2:1).

IR (Nujol): 1700 (C=O), 1545 cm^{-1} (C=C).

^{1}H NMR (400 MHz, $CDCl_3$): δ (NH form) = 7.64 (s, 1 H), 4.31 (q, 2 H), 1.57 (s, 6 H), 1.49 (s, 6 H), 1.34 (t, 3 H).

^{77}Se NMR: δ = 545.

MS (EI): *m*/*z* (%) = 316 (M^+, 5), 302 (52), 286 (100), 271 (61).

Anal. Calcd for $C_{13}H_{18}NO_3Se$: C, 49.53; H, 5.76; N, 4.44. Found: C, 49.35; H, 5.79; N, 4.31.

Acid 2b

Mp 230–232 °C; R_f = 0.20 ($CHCl_3$–MeOH, 9:1).

IR (Nujol): 3150 (OH), 1690 (C=O), 1540 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 288 (M^+, 10), 274 (36), 258 (100), 243 (77).

Anal. Calcd for $C_{11}H_{14}NO_3Se$: C, 46.00; H, 4.91; N, 4.88. Found: C, 45.93; H, 4.94; N, 4.82.

2-(Ethoxycarbonyl)-4,4,6,6-tetramethyl-5,6-dihydro-4*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl Radical (2a) (Method B)

To a soln of **2b** (576 mg, 2.0 mmol) and DBU (302 mg, 2.0 mmol) in anhyd MeCN (15 mL) was added EtI (312 mg, 2.0 mmol) and the soln remained at r.t. for 12 h. The solvents were evaporated in vacuo and the residue was partitioned between 5% aq H_2SO_4 (10 mL) and EtOAc (20 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated and the residue was purified by flash column chromatography to give **2b** (497 mg, 79%) with the same physical and spectroscopic data as the compound obtained by Method A.

4,4,6,6-Tetramethyl-2-nitro-5,6-dihydro-4*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl Radical (3) and 3-Amino-4,4,6,6-tetramethyl-2-nitro-5,6-dihydro-4*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl Radical (7)

A suspension of freshly made Na_2Se (625 mg, 5.0 mmol) in DMF (10 mL) and H_2O (0.5 mL) was stirred under N_2 at 50 °C for 30 min. To this was added, in 1 portion, **1** (1.25 g, 5.0 mmol) or **5** (1.22 g, 5.0 mmol) in DMF (5 mL) and the mixture was stirred at 50 °C for 30 min. $BrCH_2NO_2$ (700 mg, 5.0 mmol) in DMF (2 mL) was added and the mixture was stirred at 50 °C for 1 h. NaOH (200 mg, 5.0 mmol) in H_2O (5 mL) was added and the mixture was stirred at 50 °C for a further 30 min. The mixture was cooled, the solvents were evaporated off in vacuo, and the residue was partitioned between EtOAc (20 mL) and H_2O (10 mL). The organic phase was separated, the aqueous phase was washed with EtOAc (20 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–Et_2O, 2:1 for **3**) or (hexane–EtOAc, 2:1 for **7**) to give the 2-nitroselenophenes.

2-Nitro Derivative 3

Orange solid; yield: 549 mg (38%); mp 199–201 °C; R_f = 0.63 (hexane–EtOAc, 2:1).

IR (Nujol): 1635 (C=C), 1500 cm^{-1} (NO_2).

MS (EI): *m*/*z* (%) = 289 (M^+, 9), 275 (10), 259 (100), 242 (50).

Anal. Calcd for $C_{10}H_{13}N_2O_3Se$: C, 41.68; H, 4.55; N, 9.72. Found: C, 41.58; H, 4.68; N, 9.64.

2-Nitro-3-amino Derivative 7

Yellow solid; yield: 163 mg (10%); mp 230–232 °C; R_f = 0.21 (hexane–EtOAc, 2:1).

IR (Nujol): 3440, 3320 (NH_2), 1610 (C=C), 1510 cm^{-1} (NO_2).

MS (EI): *m*/*z* (%) = 304 (M^+, 23), 290 (72), 274 (100), 257 (93).

Anal. Calcd for $C_{10}H_{14}N_3O_3Se$: C, 39.61; H, 4.65; N, 13.86. Found: C, 39.69; H, 4.68; N, 13.70.

2-Cyano-4,4,6,6-tetramethyl-5,6-dihydro-4*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl Radical (4) and 3-Amino-2-cyano-4,4,6,6-tetramethyl-5,6-dihydro-4*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl Radical (8)

A suspension of freshly made Na_2Se (625 mg, 5.0 mmol) in DMF (10 mL) and H_2O (0.5 mL) was stirred under N_2 at 50 °C for 30 min. To this was added in 1 portion **1** (1.25 g, 5.0 mmol for **4**) or **5** (1.22 g, 5.0 mmol for **8**) in DMF (5 mL) and the mixture was stirred at 50 °C for 30 min. Chloroacetonitrile (377 mg, 5.0 mmol) in DMF (2 mL) was added and the mixture was stirred at 50 °C for 1 h. NaOH (200 mg, 5.0 mmol) in H_2O (5 mL) was added and the mixture was stirred at 50 °C for a further 30 min. The mixture was cooled, the solvents were evaporated off in vacuo, and the residue was partitioned between EtOAc (20 mL) and H_2O (10 mL). The organic phase was separated, the aqueous phase was washed with EtOAc (20 mL) and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc, 2:1) to give the 2-selenophenecarbonitriles.

2-Cyano Derivative 4

Yellow solid; yield: 469 mg (35%); mp 150–152 °C; R_f = 0.59 (hexane–EtOAc, 2:1).

IR (Nujol): 2220 (C≡N), 1645 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 269 (M^+, 11), 255 (17), 239 (92), 224 (100).

Anal. Calcd for $C_{11}H_{13}N_2OSe$: C, 49.26; H, 4.89; N, 10.45. Found: C, 49.16; H, 5.01; N, 10.39.

3-Amino-2-cyano Derivative 8

Yellow solid; yield: 264 mg (12%); mp 104–105 °C; R_f = 0.28 (hexane–EtOAc, 2:1).

IR (Nujol): 3430, 3340 (NH_2), 2180 (C≡N), 1640 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 284 (M^+, 4), 270 (18), 254 (72), 240 (100).

Anal. Calcd for $C_{11}H_{14}N_3OSe$: C, 46.65; H, 4.98; N, 14.84. Found: C, 46.54; H, 4.85; N, 14.90.

3-Amino-2-(ethoxycarbonyl)-4,4,6,6-tetramethyl-5,6-dihydro-4*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl Radical (6)

A suspension of freshly made Na_2Se (625 mg, 5.0 mmol) in DMF (10 mL) and H_2O (0.5 mL) was stirred under N_2 at 50 °C for 30 min. To this was added in 1 portion **1** (1.25 g, 5.0 mmol) in DMF (5 mL) and the mixture was stirred at 50 °C for 30 min. Ethyl chloroacetate (612 mg, 5.0 mmol) in DMF (2 mL) was added and the mixture was stirred at 50 °C for 1 h; DBU (755 mg, 5.0 mmol) was added and the mixture was stirred at 50 °C for a further 30 min. The mixture was cooled, the solvents were evaporated off in vacuo, and the residue was partitioned between EtOAc (20 mL) and H_2O (10 mL). The organic phase was separated, the aqueous phase was washed with EtOAc (20 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc, 2:1) to give **6** (264 mg, 16%) as a yellow solid; mp 151–153 °C; R_f = 0.39 (hexane–EtOAc, 2:1).

IR (Nujol): 3470, 3380 (NH_2), 1660 (C=O), 1550 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 331 (M^+, 8), 301 (32), 255 (66), 174 (100).

Anal. Calcd for $C_{13}H_{19}N_2O_3Se$: C, 47.28; H, 5.80; N, 8.48. Found: C, 47.41; H, 5.92; N, 8.49.

2-(Hydroxymethyl)-4,4,6,6-tetramethyl-5,6-dihydro-4*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl Radical (9)

To a soln of **2a** (630 mg, 2.0 mmol) in THF (30 mL) was added dropwise at 0 °C 65% Red-Al in toluene soln (0.77 mL, 2.5 mmol) dissolved in THF (5 mL). The mixture was stirred under N_2 at r.t. for 30 min, then the mixture was poured into ice-cooled 10% aq NaOH soln (20 mL). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were dried ($MgSO_4$), PbO_2 (50 mg) was added and O_2 was bubbled through the soln for 15 min. The mixture was filtered and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc, 2:1) to give **9** (354 mg, 65%) as a yellow solid; mp 142–144 °C; R_f = 0.15 (hexane–EtOAc, 2:1).

IR (Nujol): 3400 (OH), 1640 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 274 (M^+, 6), 260 (21), 244 (100), 229 (62).

Anal. Calcd for $C_{11}H_{16}NO_2Se$: C, 48.36; H, 5.90; N, 5.13. Found: C, 48.28; H, 6.00; N, 5.10.

2-Formyl-4,4,6,6-tetramethyl-5,6-dihydro-4*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl Radical (10)

To a soln of **9** (546 mg, 2.0 mmol) in $CHCl_3$ (30 mL) was added activated MnO_2 (1.74 g, 20.0 mmol) and the mixture was stirred and heated under reflux for 1 h. The mixture was cooled and MnO_2 was filtered off; the filtrate was evaporated and purified further by flash column chromatography (hexane–EtOAc, 2:1) to give **10** (397 mg, 73%) as a yellow solid; mp 158–160 °C; R_f = 0.41 (hexane–EtOAc, 2:1).

IR (Nujol): 1660 (C=O), 1645 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 272 (M^+, 6), 258 (23), 242 (100), 227 (56).

Anal. Calcd for $C_{11}H_{14}NO_2Se$: C, 48.72; H, 5.20; N, 5.16. Found: C, 48.73; H, 5.25; N, 5.22.

4,4,6,6-Tetramethyl-2-vinyl-4,6-dihydro-5*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl Radical (11)

A soln of **10** (544 mg, 2.0 mmol), $MePh_3PI$ (808 mg, 2.0 mmol), K_2CO_3 (276 mg, 2.0 mmol), powdered KOH (11 mg, 0.2 mmol), and 18-crown-6 (5.0 mg) in dioxane (20 mL) was stirred and heated under reflux for 48 h. The mixture was cooled and the inorganic salts were filtered off; the residue was partitioned between H_2O (10 mL) and Et_2O (20 mL) and the aqueous phase was washed with Et_2O (20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–Et_2O, 2:1) to afford **11** (317 mg, 59%) as a deep yellow solid; mp 88–90 °C; R_f = 0.43 (hexane–Et_2O, 2:1).

IR (Nujol): 1615, 1560 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 270 (M^+, 6), 240 (93), 225 (100), 129 (64).

Anal. Calcd for $C_{12}H_{16}NOSe$: C, 53.54; H, 5.99; N, 5.20. Found: C, 53.48; H, 5.88; N, 5.09.

2-(Chloromethyl)-4,4,6,6-tetramethyl-4,6-dihydro-5*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl Radical (12)

To stirred soln of **9** (548 mg, 2.0 mmol) and Et_3N (222 mg, 2.2 mmol) in CH_2Cl_2 (20 mL) was added dropwise at 0 °C MsCl (252 mg, 2.2 mmol) dissolved in CH_2Cl_2 (5 mL). The mixture was stirred at r.t. for 30 min and washed with H_2O (10 mL) and the organic phase was separated, dried, filtered, and evaporated. The residue was dissolved in acetone (10 mL), LiCl (172 mg, 4.0 mmol) was added, and the mixture was stirred and heated under reflux for 40 min. The mixture was cooled, the solvent was evaporated off in vacuo and the residue was partitioned between Et_2O (20 mL) and H_2O (10 mL). The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–Et_2O, 2:1) to give **12** (280 mg, 48%) as a yellow solid; mp 58–59 °C; R_f = 0.24 (hexane–Et_2O, 2:1).

IR (Nujol): 1645 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 292 (M^+, 9), 278 (32), 262 (100), 247 (55).

Anal. Calcd for $C_{11}H_{15}ClNOSe$: C, 45.30; H, 5.18; N, 4.80. Found: C, 45.22; H, 5.10; N, 4.60.

This compound is stable at –18 °C for several weeks.

4,4,6,6-Tetramethyl-2-{[(methylsulfonyl)thio]methyl}-4,6-dihydro-5*H*-selenolo[2,3-*c*]pyrrol-5-yloxyl Radical (14)

To a stirred mixture of **9** (741 mg, 3.0 mmol) and CBr_4 (1.33 g, 4.03 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added a soln of Ph_3P (1.32 g, 5.03 mmol) in CH_2Cl_2 (3 mL); the mixture was stirred at 0 °C for 30 min. The mixture was then dried on silica gel in vacuo (the bath temperature <30 °C) and filtered through silica gel plug collecting the unreacted Ph_3P (hexane) and **13** (hexane–Et_2O, 2:1). The collected crude product (364 mg, 36%) was treated with $NaSSO_2Me$ (268 mg, 2.0 mmol) dissolved in a mixture of acetone (10 mL) and H_2O (5 mL). The mixture was allowed to stay at 50 °C and after consumption of **13** (monitored by TLC, ~45 min), $CHCl_3$ (20 mL) and brine (10 mL) were added. The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography (hexane–EtOAc, 2:1) to yield **14** (104 mg, 33%) as a pale yellow solid; mp 132–133 °C; R_f = 0.16 (hexane–EtOAc, 2:1).

IR (Nujol): 1640 cm^{-1} (C=C).

MS (EI): *m*/*z* (%) = 368 (M^+, 3), 338 (27), 258 (73), 227 (100).

Anal. Calcd for $C_{12}H_{18}NO_3S_2Se$: C, 39.23; H, 4.94; N, 3.81; S, 17.45. Found: C, 39.15; H, 5.03; N, 3.62; S, 17.22.

2-[(4,4,6,6-Tetramethyl-5-oxyl-4,6-dihydro-5*H*-selenolo[2,3-*c*]pyrrol-2-yl)methylthio]quinazolin-4(3*H*)-one Radical (15)

To a stirred soln of 2-mercaptoquinazolin-4(3*H*)-one (178 mg, 1.0 mmol) in DMF (7 mL) was added K_2CO_3 (138 mg, 1.0 mmol) and the mixture was stirred at r.t. for 15 min, then freshly prepared **13** (~1.0 mmol as described above) in DMF (3 mL) was added in 1 portion and the mixture was stirred and heated at reflux temperature for 3 h. The mixture was cooled, $CHCl_3$ (20 mL) was added, and inorganic salts were filtered off. The filtrate was evaporated and the residue was re-dissolved in $CHCl_3$ (20 mL) and washed with H_2O (10 mL) and the organic phase was separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography ($CHCl_3$–Et_2O, 2:1) to give **15** (177 mg, 42%) as a yellow solid; mp 194–195 °C; R_f = 0.42 ($CHCl_3$–Et_2O, 2:1).

IR (Nujol): 3120 (NH), 1675 (C=O), 1600, 1585 cm^{-1} (C=C).

MS (ESI): *m*/*z* = 457 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{20}N_3O_2SSe$: C, 52.65; H, 4.65; N, 9.70; S, 7.40. Found: C, 52.55; H, 4.44; N, 9.81; S, 7.18.

***tert*-Butyl *rac*-2-Amino-3-(4,4,6,6-tetramethyl-5-oxyl-4,6-dihydro-5*H*-selenolo[2,3-*c*]pyrrol-2-yl)propanoate Radical (16)**

To stirred soln of *N*-(diphenylmethylene)glycine *tert*-butyl ester (295 mg, 1.0 mmol) and freshly made **13** (~1.0 mmol) in CH_2Cl_2 (20 mL) was added 10% aq NaOH (3 mL) followed by addition of Bu_4NHSO_4 (169 mg, 0.5 mmol) and the mixture was stirred at r.t. for 2 h. The organic phase was separated, dried ($MgSO_4$), filtered, and evaporated to give the crude imine which was immediately subjected to acidic hydrolysis. The residue was dissolved in EtOH (10 mL), 5% aq H_2SO_4 (3 mL) was added and the mixture was allowed to stand at r.t. (TLC monitoring). After consumption of the Schiff base (~30 min), H_2O (10 mL) was added and the pH was adjusted with solid K_2CO_3 until pH 8. The mixture was extracted with $CHCl_3$ (2 × 20 mL) and the combined organic phases were separated, dried ($MgSO_4$), filtered, and evaporated. The residue was purified by flash column chromatography ($CHCl_3$–MeOH, 9:1) to give **16** (177 mg, 46%) as a yellow solid; mp 92–94 °C; R_f = 0.57 ($CHCl_3$–MeOH, 9:1).

IR (Nujol): 3480, 3420 (NH_2), 1730 (C=O), 1650, 1620 cm^{-1} (C=C).

MS (ESI): *m*/*z* = 388 $[M + H]^+$.

Anal. Calcd for $C_{17}H_{27}N_2O_3Se$: C, 52.85; H, 7.04; N, 7.25. Found: C, 52.78; H, 7.16; N, 7.33.

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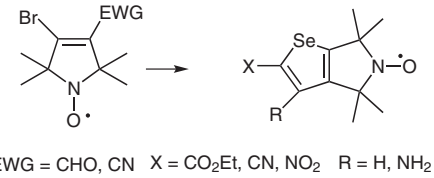

EWG = CHO, CN X = CO_2Et, CN, NO_2 R = H, NH_2

graphical abstract