

# On the preparation of 1,2,5-selenadiazolo [3,4-*e*]indole and its [3,4-*f*] and [3,4-*g*] isomers through the Batcho–Leimgruber indole synthesis

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(received 25 Feb 01; accepted 08 Nov 01; published on the web 16 Nov 01)

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## Abstract

1,2,5-Selenadiazolo[3,4-*e*]indole **6** was prepared by applying the Batcho–Leimgruber indole synthesis on 4-methyl-5-nitro-2,1,3-benzoselenadiazole **9**. This methodology was unsuccessful when applied to 5-methyl-6-nitro-2,1,3-benzoselenadiazole **14** for the synthesis of 1,2,5-selenadiazolo[3,4-*f*]indole **5**. An improvement on the preparation of 1,2,5-selenadiazolo[3,4-*g*]indole **3** is reported. An initial study on the bromination of **3** and the <sup>77</sup>Se-NMR chemical shifts of **3** and **6**, and of their precursors are presented.

**Keywords:** Batcho-Leimgruber indole synthesis, 1,2,5-selenadiazolo[3,4-*e*]indole, <sup>77</sup>Se-NMR

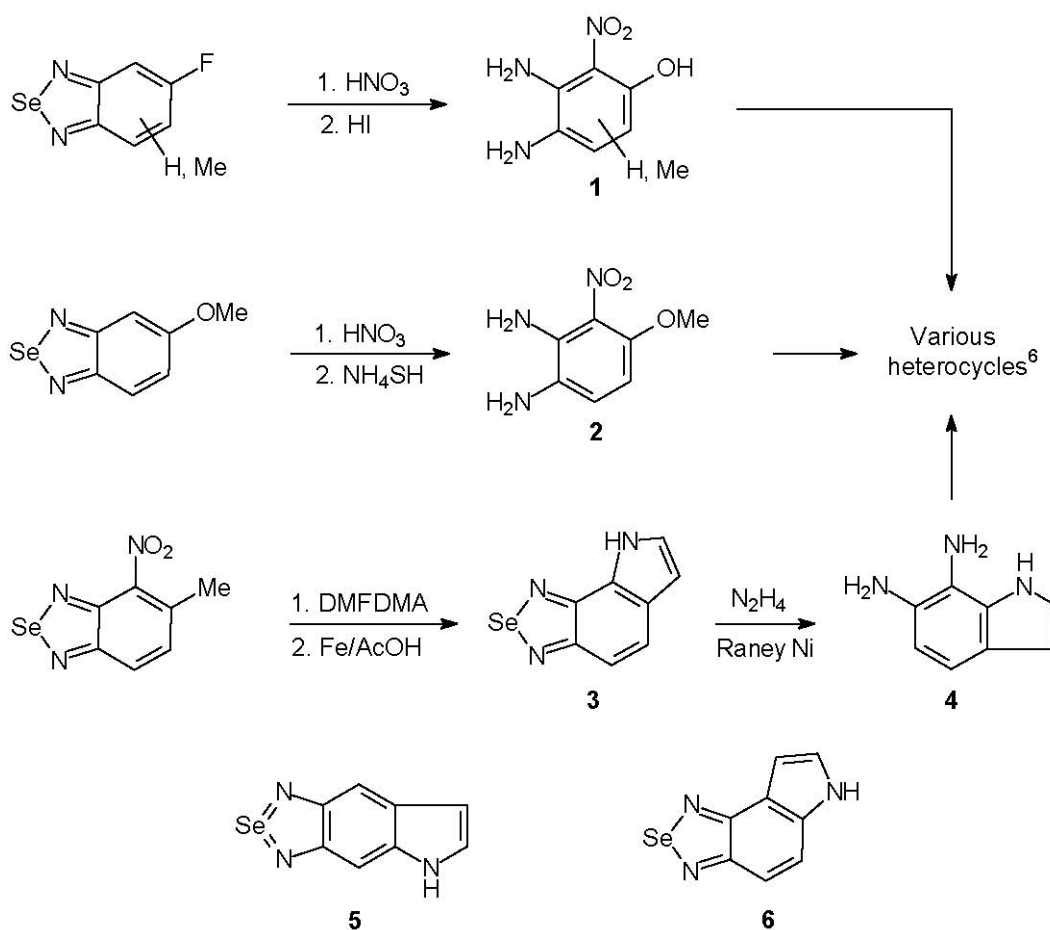
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## Introduction

Derivatives of 1,2,5-selenadiazolobenzene (2,1,3-benzoselenadiazole, bsd) find plenty of pharmaceutical and other industrial applications, and they have also proved to be useful synthetic intermediates.<sup>1,2</sup> For example, the versatile diaminonitrophenols **1**<sup>3</sup> (Scheme 1), 4-methoxy-3-nitro-1,2-benzenediamine **2**<sup>4</sup> and indole-6,7-diamine **4**<sup>5</sup> are easily obtained by reductive deselenation of the corresponding bsd and then converted into other heterocycles.<sup>3–6</sup> In connection to our recent synthesis of selenadiazoloindole **3**<sup>5</sup> via the Batcho–Leimgruber (B–L) methodology,<sup>7</sup> we now report on our attempts to synthesize the unknown linear isomer 1,2,5-selenadiazolo[3,4-*f*]indole **5** and the angular isomer 1,2,5-selenadiazolo[3,4-*e*]indole **6** by applying the B–L method on the corresponding methylnitro-bsd.

## Results and Discussion

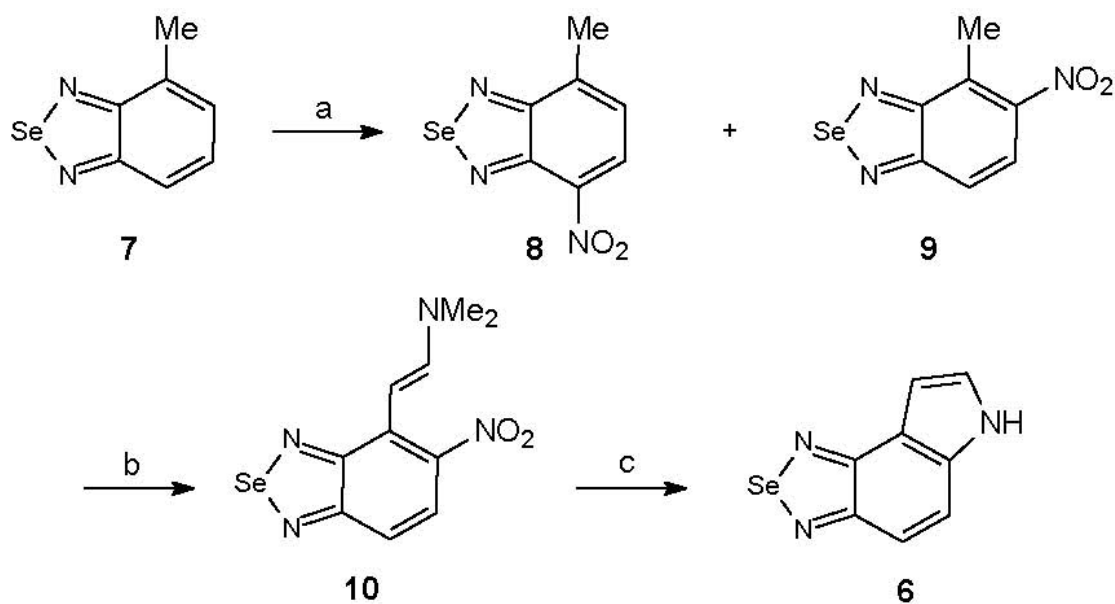
The title [3,4-*e*]-isomer **6** could be obtained from the readily available 4-methyl-bsd **7**<sup>8</sup> (Scheme 2). Nitration of **7** gave a mixture of 4-methyl-7-nitro-bsd **8**<sup>9</sup> and the 5-nitro isomer **9**<sup>9</sup>. The formation ratio of **8** and **9** could be influenced by varying the nitration conditions. For instance, treatment of a solution of **7** in 95% H<sub>2</sub>SO<sub>4</sub> with an AcOH–fuming HNO<sub>3</sub> mixture afforded **8** and **9** in a 3:2 ratio at 75 °C. This ratio was inverted to 2:3 when a solution of **7** in 80% H<sub>2</sub>SO<sub>4</sub> was treated with 80% H<sub>2</sub>SO<sub>4</sub>–65% HNO<sub>3</sub> at ≤ 20 °C. Separation of **8** and **9** was accomplished by fractional recrystallization from acetonitrile or toluene, and by steam distillation of the 2:3 mixture followed by one recrystallization to afford analytically pure **9**, which was then exposed to the B–L indole synthesis.



Scheme 1

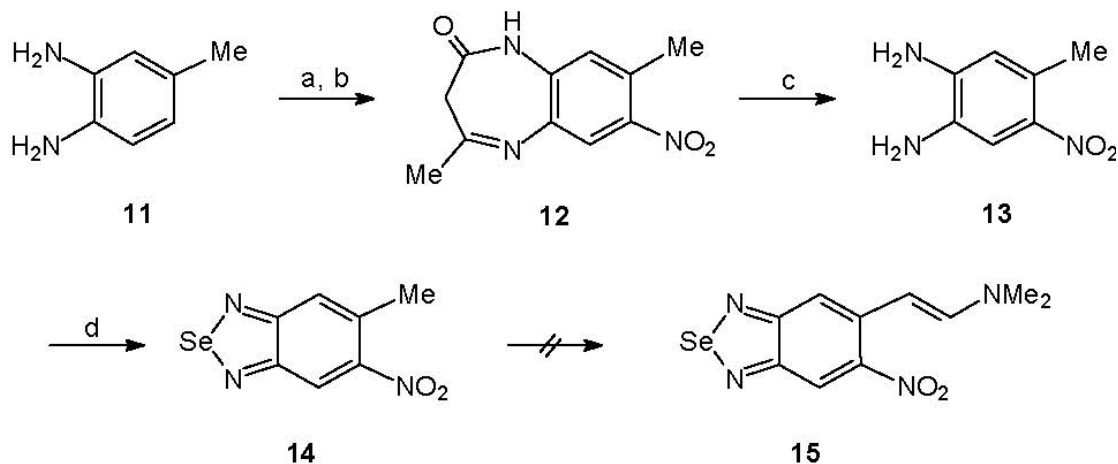
Treatment of **9** with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) gave enamine **10** (blue coloured in chloroform), which was isolated and characterized as the *trans* isomer ( $J = 12.5$  Hz). The  $^{13}\text{C}$ -NMR signal from the *N*-methyl groups could only be detected at higher temperatures ( $\geq 80$  °C) presumably due to hindered rotation. The reductive ring closure of **10** into the title compound **6** was best accomplished by heating with Fe powder in toluene–glacial AcOH in the presence of silica gel, albeit in no more than 20% isolated yield. No better results were obtained under other reductive ring closure conditions such as hydrogenation over Pd-C or Raney nickel at various temperatures and pressures, or treatment with  $\text{N}_2\text{H}_4$  hydrate and Raney nickel in various solvents. Further, attempts using  $\text{Na}_2\text{S}_2\text{O}_4$  or  $\text{TiCl}_3$  were not successful either.<sup>5,10</sup> Applying the B–L indole synthesis to a mixture of the nitro-bsd derivatives **8** and **9** did not alter the formation yield of the title [3,4-*e*] isomer **6**.

The conversion of **9** into **10** was less efficient than the recently reported<sup>5</sup> conversion of 4-nitro-5-methyl-bsd into (*E*)-5-[2-(dimethylamino)ethenyl]-4-nitro-bsd (red in chloroform) leading to the title [3,4-*g*] isomer **3**.<sup>5</sup> Addition of column chromatography silica gel<sup>11</sup> in the Fe powder-reduction of (*E*)-5-[2-(dimethylamino)ethenyl]-4-nitro-bsd<sup>5</sup> did not improve the yield (50–55%) but made the work-up of **3** much more convenient; this preferable procedure is therefore described in this paper.



**Scheme 2.** (a) 80%  $\text{H}_2\text{SO}_4$ , 65%  $\text{HNO}_3$ ,  $0 \rightarrow \leq 20$  °C; (b) DMFDMA, MeCN, reflux, 5 h; (c) Fe, silica, PhMe/glacial AcOH (5:3 v/v), reflux 1 h

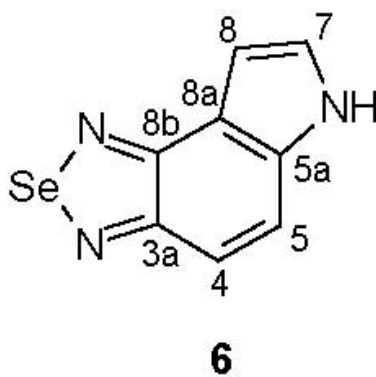
Preparation of the unknown linear [3,4-*f*] isomer **5** was attempted by applying the B-L reaction on 5-methyl-6-nitro-bsd **14** (Scheme 3). This derivative was prepared by treatment of 4-methyl-1,2-benzenediamine **11** with ethyl acetoacetate and subsequent nitration of the formed diazepinone to **12**, which on hydrolysis afforded **13**.<sup>12</sup> Treatment of the latter with SeO<sub>2</sub> afforded **14**, which has also been obtained from 5-methyl-2,4-dinitroaniline.<sup>13</sup>



**Scheme 3.** (a) AcCH<sub>2</sub>CO<sub>2</sub>Et, *o*-xylene, reflux, 16 h; (b) conc. H<sub>2</sub>SO<sub>4</sub>, NaNO<sub>3</sub>, -10 °C → rt; (c) MeOH/5.5 M HCl (1:1 v/v), reflux, 5 h; (d) aq. SeO<sub>2</sub>, 1 M HCl, 85 °C

In contrast to the conversion of **9** into **10**, treatment of **14**<sup>12,13</sup> with DMFDMA in refluxing CH<sub>3</sub>CN gave no traces of enamine **15**. After prolonged reaction time, unchanged starting material could still be recovered together with unidentified material. Neither the use of DMF as solvent, nor addition of pyrrolidine<sup>10</sup> would facilitate the formation of **15**, presumably because of fixation of the C5–C6 bond and thus no stabilization of the enamine by the nitro group.

Proton- and carbon-NMR data for the two angular isomers **3** and **6** are collected in Table 1.



**Table 1.**  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR shifts and HMBC correlations for **3** and **6**

Compound	$^{13}\text{C}$ index	$^1\text{H}$ index	$\delta_{\text{H}}$ (ppm)	$\delta_{\text{C}}$ (ppm)	HMBC cross peaks <sup>a</sup>
<b>3</b>	3a			159.5	$^3J_{\text{C-H5}}, ^2J_{\text{C-H4}}$
	4	4	7.31	115.1	$^2J_{\text{C-H5}}, ^1J_{\text{C-H4}}$
	5	5	7.73	126.8	$^1J_{\text{C-H5}}$
	5a			125.7	$^3J_{\text{C-H7}}, ^3J_{\text{C-H4}}$
	6	6	6.57	104.5	$^4J_{\text{C-H4}}, ^3J_{\text{C-H5}}, ^2J_{\text{C-H7}}, ^1J_{\text{C-H6}}$
	7	7	7.36	124.5	
		8	12.5		
	8a			124.6	$^3J_{\text{C-H5}}, ^3J_{\text{C-H7}}, ^3J_{\text{C-H6}}$
	8b			150.7	$^4J_{\text{C-H5}}, ^3J_{\text{C-H4}}$
<b>6</b>	3a			155.7	$^3J_{\text{C-H5}}, ^2J_{\text{C-H4}}$
	4	4	7.68	120.1	$^2J_{\text{C-H5}}, ^1J_{\text{C-H4}}$
	5	5	7.38	116.1	$^1J_{\text{C-H5}}$
	5a			118.2	$^3J_{\text{C-H4}}, ^3J_{\text{C-H7}}, ^3J_{\text{C-H8}}, ^2J_{\text{C-H5}}$
		6	11.8		
	7	7	7.35	123.6	$^2J_{\text{C-H8}}$
	8	8	6.93	104.2	$^4J_{\text{C-H5}}, ^2J_{\text{C-H7}}, ^1J_{\text{C-H8}}$
	8a			133.1	$^3J_{\text{C-H5}}, ^3J_{\text{C-H7}}, ^2J_{\text{C-H8}}$
	8b			158.7	$^3J_{\text{C-H4}}$

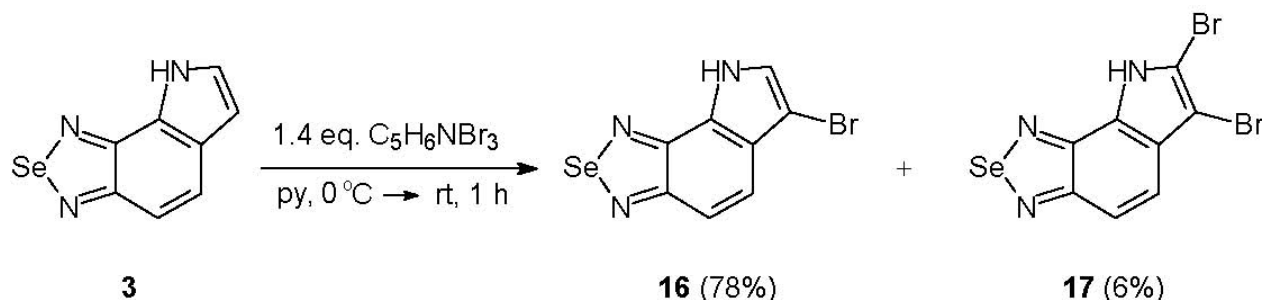
<sup>a</sup>  $^nJ_{\text{C-HX}}$  denotes the heteronuclear coupling ( $n = 1-4$ ) between the indexed carbon and proton X.

The  $^{77}\text{Se}$ -NMR chemical shifts of **3** and **6** and their precursors are shown in Table 2.  $^{77}\text{Se}$ -NMR chemical shifts of other bsd derivatives were recently reported.<sup>1</sup>

**Table 2.**  $^{77}\text{Se}$ - NMR chemical shifts

Compound	$\delta_{\text{Se}}$ (ppm)
5-Methyl-4-nitro-2,1,3-benzoselenadiazole <sup>5</sup>	1557.8
( <i>E</i> )-5-[2-(Dimethylamino)ethenyl]-4-nitro-bsd <sup>5</sup>	1526.3
1,2,5-Selenadiazolo[3,4- <i>g</i> ]indole <b>3</b> <sup>5</sup>	1498.1
1,2,5-Selenadiazolo[3,4- <i>e</i> ]indole <b>6</b>	1497.6
4-Methyl-5-nitro-2,1,3-benzoselenadiazole <b>9</b>	1571.5
( <i>E</i> )-4-[2-(Dimethylamino)ethenyl]-5-nitro-bsd <b>10</b>	1534.6
5-Methyl-6-nitro-2,1,3-benzoselenadiazole <b>14</b>	1585.1

Initial monobromination studies on the title compound **3** with various amounts pyridinium tribromide in pyridine were performed at 0 °C → 20 °C. When no more than 1.4 equivalents of brominating agent were used, the 6-bromo derivative **16**<sup>14</sup> (Scheme 4) and the 6,7-dibromo derivative **17**<sup>14</sup> were formed within 1 hour in a 14:1 ratio and in 84% yield. Treatment with 1.7 equivalents of  $\text{C}_5\text{H}_6\text{NBr}_3$  afforded **16** in 50% and **17** in 25% yield within 2 hours, while use of 1.2 equivalents of brominating agent gave no dibromo derivative, 71% of **16** and 18% of unreacted **3** after 13 hours.

**Scheme 4**

## Experimental Section

**General Procedures.** Analytical TLC was performed using aluminium plates precoated with silica gel 60 F<sub>254</sub> (Merck) and visualized by UV light and Van Urk's reagent.<sup>15</sup> Flash chromatography was carried out on silica gel 60 (35–70 μ, Grace). Melting points (uncorrected) were determined on a Büchi Melting Point B-545. All NMR spectra were recorded on a Bruker DPX 300 spectrometer at 25 °C, unless otherwise stated.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR signals were

referenced to the solvent ( $(\text{CD}_3)_2\text{SO}$   $\delta_{\text{H}}$  2.50 and  $\delta_{\text{C}}$  39.5). Gradient HMBC and HMQC experiments were used for the assignments. Coupling constants are given in Hz and without sign. In  $^{77}\text{Se}$ -NMR experiments, saturated aqueous selenous acid was used as an external reference (11.5 M,  $\text{H}_2\text{SeO}_3$   $\delta_{\text{Se}}$  1300.47)<sup>16</sup> and the samples were dissolved in and locked on  $(\text{CD}_3)_2\text{SO}$ . The IR-spectra were recorded (KBr) on a Perkin–Elmer FT-IR 1600 instrument. Electrospray-MS were recorded on a Perkin–Elmer API 150Ex spectrometer. Elemental composition was determined by EI-HRMS on a JEOL JMS-SX/SX102A instrument with direct insertion at 70 eV and an ion source temperature of 200 °C.

**Materials.** Unless otherwise stated, these were commercial samples. All organic solvents were of analytical quality and used as purchased. Solvent mixtures are defined by volume ratios (v/v).

**1,2,5-Selenadiazolo[3,4-g]indole (3).** A vigorously magnetically stirred, dark red mixture of (*E*)-5-[2-(dimethylamino)ethenyl]-4-nitro 2,1,3-benzoselenadiazole<sup>5</sup> (2.20 g, 7.37 mmol), iron powder (6.99 g, 125 mmol) and silica gel (column chromatography grade, 35–70 mesh, 18.4 g) in toluene/glacial acetic acid 5:3 (100 mL) was cautiously heated under a nitrogen atmosphere. The reaction mixture turned brown and viscous before the temperature reached the boiling point; heating was discontinued. The mixture was allowed to cool to room T, diluted with ether and left stirred before being filtered first under vacuum and a second time by gravitation. The filtrate was washed successively with aqueous sodium disulfite, water, saturated sodium bicarbonate solution and brine. Drying ( $\text{MgSO}_4$ ) and concentration gave indole **3** as a yellow solid (0.85 g, 52%). Its MS and  $^1\text{H}$ -NMR data were in accordance to those previously reported.<sup>5</sup> For  $^{13}\text{C}$ -NMR data see Table 1.

**1,2,5-Selenadiazolo[3,4-e]indole (6).** A vigorously magnetically stirred mixture of enamine **10** (97 mg, 0.33 mmol), iron powder (0.31 g, 5.53 mmol) and silica gel (column chromatography grade, 35–70 mesh, 0.81 g) in toluene/glacial acetic acid 5:3 (5 mL) was cautiously heated to reflux under nitrogen for 1 h. The reaction mixture was allowed to cool to room T, diluted with chloroform and filtered. The filter-cake was washed with chloroform and then ether. The filtrate was washed successively with aqueous sodium disulfite, saturated sodium bicarbonate solution until pH 8 and brine. Drying ( $\text{Na}_2\text{SO}_4$ ), concentration onto silica and flash chromatography (hexane/EtOAc gradient 5:1–2:1) gave **6** as an orange solid (14 mg, 19%). Recrystallization from acetonitrile gave brown-yellow crystals of mp 171–2 °C;  $^1\text{H}$  NMR  $\delta$  11.8 (1H, br s, *N*-H), 7.68 (1H, d,  $J = 9.3$ , 4-H), 7.36 (2H, m, 5-H and 7-H), 6.93 (1H, d,  $J = 2.84$ , 8-H);  $^{13}\text{C}$  NMR: see Table 1; IR  $\nu$  3286, 3170, 3101, 1591, 1563, 1501, 1417, 1351, 1316, 896, 801, 745, 724  $\text{cm}^{-1}$ ; MS  $m/z$ : 224 ( $\text{MH}^+$ ); EI-HRMS ( $\text{M}^+$ ) calcd for  $\text{C}_8\text{H}_5\text{N}_3\text{Se}$  222.9649, found 222.9637.

**4-Methyl-7-nitro-2,1,3-benzoselenadiazole (8).** Recrystallization from toluene (see below) afforded **8** as golden-yellow needles: mp 235 °C (subl.) [lit.<sup>9</sup> 242 °C];  $^1\text{H}$ -NMR  $\delta$  8.42 (1H, d,  $J$

= 7.5, 6-H), 7.52 (1H, dd,  $J = 7.5, 1.1$ , 5-H), 2.71 (3H, d,  $J = 0.8$ , Me);  $^{13}\text{C-NMR}$   $\delta$  160.4 (3a-C), 150.2 (7a-C), 140.9 (4-C), 139.2 (7-C), 127.9 (6-C or 5-C), 125.4 (5-C or 6-C), 18.8 (Me); IR  $\nu$  3055, 2978, 1611, 1510, 1332, 858, 824, 768, 733  $\text{cm}^{-1}$ .

**4-Methyl-5-nitro-2,1,3-benzoselenadiazole (9).** A 3:2 mixture of the *ortho*- and *para*-nitro isomers was obtained by nitration<sup>9</sup> of 4-methyl-2,1,3-benzoselenadiazole.<sup>8</sup> The steam distillate of the crude mixture afforded **8** and **9** in a 1:16 ratio. Recrystallization of the evaporation residue from toluene furnished **9** as a pale yellow powder of mp 171–2 °C [lit.<sup>9</sup> 157.5–8.0 °C];  $^1\text{H-NMR}$   $\delta$  8.00 (1H, d,  $J = 9.7$ , 6-H), 7.84 (1H, dd,  $J = 9.7, 0.6$ , 7-H), 2.85 (3H, s, Me);  $^{13}\text{C-NMR}$   $\delta$  159.01 (3a-C and 7a-C), 147.46 (5-C), 129.17 (4-C), 123.73 (6-C), 121.28 (7-C), 14.97 (Me); IR  $\nu$  3082, 1601, 1553, 1509, 1380, 1360, 1342, 1277, 827, 812, 741, 714  $\text{cm}^{-1}$ .

**(E)-4-[2-(Dimethylamino)ethenyl]-5-nitro-2,1,3-benzoselenadiazole (10).** DMFDMA (92%, 2.10 mL, 14.5 mmol) was added dropwise from a syringe to a stirred slurry of **9** (1.67 g, 6.87 mmol) in acetonitrile (25 mL) at room T, under nitrogen and in oven-dried and septum-capped glassware. The mixture was heated to reflux for 3 h. More DMFDMA (92%, 2.00 mL, 13.8 mmol) was added. After 2 h at reflux, the reaction mixture was allowed to cool to room T and was allowed to stand. The precipitate was filtered off, washed with a small amount of ice-cold methanol and dried to give enamine **10** as dark brown crystals (0.76 g). Flash chromatography (hexane/EtOAc 2:1) of the evaporation residue from the mother liquor and collection of the blue band gave another 0.20 g of **10** (total yield 47%). Recrystallization of a sample from acetonitrile afforded sparkling, almost black needles of mp 165–6 °C;  $^1\text{H-NMR}$   $\delta$  9.06 (1H, d,  $J = 12.5$ , 2'-H), 7.98 (1H, d,  $J = 9.8$ , 6-H), 7.05 (1H, d,  $J = 9.8$ , 7-H), 6.77 (1H, d,  $J = 12.5$ , 1'-H), 3.11 (6H, s, *N*-Me);  $^{13}\text{C-NMR}$  ( $T = 80$  °C)  $\delta$  160.3 (7a-C), 157.7 (3a-C), 155.9 (2'-C), 136.4 (5-C), 132.6 (4-C), 126.4 (6-C), 112.4 (7-C), 91.9 (1'-C), 40.46 (*N*-Me<sub>2</sub>); IR  $\nu$  3082, 2913, 1595, 1532, 1474, 1408, 1388, 1296, 1228, 1208, 1094, 827, 806  $\text{cm}^{-1}$ .

**5-Methyl-6-nitro-2,1,3-benzoselenadiazole (14).** To a stirred, red solution of diamine **13**<sup>12</sup> (3.58 g, 21.4 mmol) in 1 M HCl (75 mL) at 85 °C was added aqueous selenium dioxide (1.33 M, 32.2 mL, 42.8 mmol) in portions. After the last addition, TLC (hexane/EtOAc 2:1) showed complete consumption of the starting material. The reaction mixture was cooled, filtered, washed with plenty of water and dried to give **14** as a light brown solid (4.1 g, 79%). A small sample was recrystallized from ethyl acetate: mp 165–6 °C [lit.<sup>13</sup> 165–6 °C];  $^1\text{H-NMR}$   $\delta$  8.51 (1H, s, 7-H), 7.91 (1H, d,  $J = 0.5$ , 4-H), 2.52 (3H, d,  $J = 0.7$ , Me);  $^{13}\text{C-NMR}$   $\delta$  159.5 (3a-C), 156.6 (7a-C), 151.2 (6-C), 130.8 (5-C), 124.5 (4-C), 118.9 (7-C), 18.9 (Me); IR  $\nu$  3102, 1610, 1528, 1491, 1385, 1339, 1281, 823, 764  $\text{cm}^{-1}$ .



## Acknowledgements

We thank the Swedish Council for Forestry and Agricultural Research (SJFR), the National Institutes of Health (USA) and the Lawrence Livermore National Laboratory for financial support.

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14. **16**. <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ 12.9 (1H, br s, *N*-H), 7.58 (2H, m, 7-H and 4-H or 5-H), 7.43 (1H, d, *J* = 9.3, 5-H or 4-H); <sup>13</sup>C-NMR (DMSO-*d*<sub>6</sub>) δ 159.4, 150.0, 125.7, 124.1, 123.6, 123.2, 116.3, 91.9. **17**: <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) δ 13.8 (1H, br s, *N*-H), 7.55 (1H, d, *J* = 9.3, 4-

H or 5-H), 7.45 (1H, d,  $J = 9.3$ , 5-H or 4-H).

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