SYNTHESIS OF SELENOPSILOCINE (3-DIMETHYLAMINOETHYL-4-HYDROXYBENZO[*b*]SELENOPHENE)

Abdelmjid Dari, Léon E. Christiaens, and Marcel J. Renson,*
Heterocyclic Chemistry, Institute of Organic Chemistry, B.6.
University of Liège, Sart-Tilman, 4000 LIEGE, Belgium

Abstract — *Starting from the known 6-methoxyanthranilic acid (5), we have synthesized in six steps the selenium analogue of psilocine (1c). The key intermediate is the 4-methoxyselenoindoxyl (8), which is condensed with the dimethylaminocarbamoylmethylenetriphenylphosphorane to give the aromatic amide (9a). Its reduction with lithium aluminium hydride leads to the methoxyamine (9b) which is finally demethylated by sodium ethanethiolate to 1c.*

INTRODUCTION

Several benzo[*b*]selenophene analogues of natural products have already been described.[1] As psilocine (**1a**) and its sulfur analogue (**1b**) display hallucinogen activity,[2-5] it is of interest to synthesize the selenium analogue "selenopsilocine" (**1c**). Indeed, selenoorganic compounds have been shown to be active in widely varying areas such as inflammation,[6] enzymology [6] or plant growth hormones.[7]

DISCUSSION AND RESULTS

The strategy consisting[8,9] of a short-step synthesis of an intermediate 4-substituted benzo[*b*]selenophene from 2-methoxyphenylpropiolic acid and selenium tetrabromide caused many difficulties. Therefore we tried to synthesize 4-methoxyselenoindoxyl (**8**) which could lead easier[1] to 3,4-disubstituted benzo[*b*]selenophenes. The synthesis of a conveniently trisubstituted selenium precyclic intermediate was not easy and was firstly tried through ortho-lithiation reactions of disubstituted derivatives.

a) Ortho-lithiation of 3-methylselenoanisole

When metallated (BuLi or LDA), 3-methylselenoanisole [10] affords poor yields of the corresponding benzaldehyde (**2a**) (DMF, 10 %) or benzoic acid (**2b**) (CO_2; 7 %). Under electrophilic acylation conditions (Ac_2O, $AlCl_3$) 2-methoxy-4-methylselenoacetophenone was isolated (2 %). Aldehyde (**2a**) undergoes classical transformations[1] to give successively in poor yields the unknown 2-carboxy-4-methoxybenzo[*b*]selenophene (**3a**) and 4-methoxybenzo[*b*]selenophene (**3b**).

b) Selenium fixation through ortholithiation reactions

The ortholithiation of *o*-anisic derivatives is not hardly regiospecific, both the ether and the protected acid being ortho directing groups.[11] Nevertheless benzamide (**4a**) is isolated in a 32 % yield from ortho-lithiation and selenation (s-BuLi,$(MeSe)_2$) of 2-methoxy-*N*,*N*-diethylbenzamide. Unfortunately, the hydrolysis of **4a** never gives acid (**2b**) (drastic conditions result in the loss of selenium). A more hydrolysable amide group recently described[12] gives under the same conditions a 10 % yield of acid (**2b**) after hydrolysis of the rapidly purified amide (**4b**).

c) Selenium fixation through seleno-dediazoniation

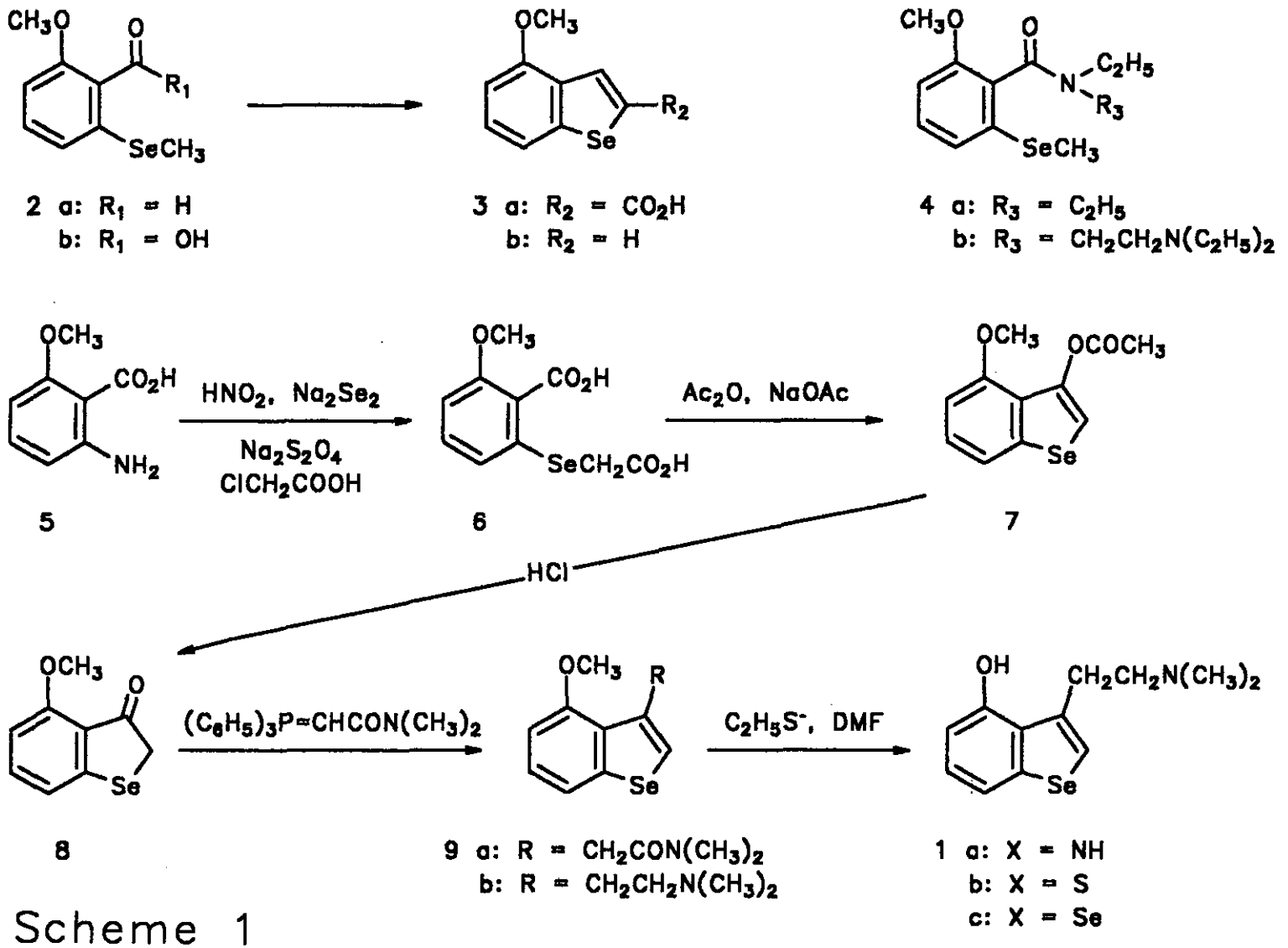
These rather disappointing results lead us to consider the more classical seleno-dediazoniation reaction from a trisubstituted precursor obtained by this fact from a longer route. The starting material,

6-methoxyanthranilic acid (5), is obtained through two different pathways. The first one (6 steps) starting from 2,6-dinitrotoluene, involves the well known reactions of oxidation and nucleophilic substitution by methanolate anion.[13] The second one (3 steps) consists of a two steps analogy with recent *o*-lithiation reactions of carbamates.[14] The diazonium salt of acid (5) is treated with Na_2Se_2[15] and the resulting rather unstable diselenide is not isolated but directly transformed[16] into the diacid (6) (64 % from 5). The following Perkin-like cyclisation affords 4-methoxyselenoindoxylacetate (7). Careful hydrolysis of ester (7) leads to the key selenoindoxyl (8) (experimental conditions must be followed strictly otherwise mixtures of highly coloured products, probably methoxyselenoindigo derivatives are formed). Ketonic form predominates in 4-methoxyselenoindoxyl in the solid form (ir, KBr) as well as in solution (ir, $CHCl_3$). The enol form appears slowly in more polar solvents (DMSO-d6, ^1H nmr) reaching a maximum of 40 % at the equilibrium. The dimethylcarbamoylmethylene-triphenylphosphorane, a rather unstable phosphorylide, reacts with ketone (8) giving the rearranged amide (9a). Its reduction by $LiAlH_4$ affords the amine (9b). Finally, selenopsilocine (1c) is formed through a nucleophilic demethylation reaction of 9b with ethanethiolate in DMF. The target molecule 1c is fully characterized.

Preliminary pharmacological results indicate a strong binding with serotoninergic sites.

EXPERIMENTAL

Solvents (C.P.) and products are from Janssen Chimica. All isolated products are pure on tlc (at least two elution systems). The usual work-up consists of pouring the reaction mixture in diluted HCl, extraction with CH_2Cl_2, washing with 10 % Na_2CO_3 if necessary , drying on $MgSO_4$ and


CH3O
O
R1
SeCH3
2 a: R1 = H
b: R1 = OH
OCH3
R2
Se
3 a: R2 = CO2H
b: R2 = H
CH3O
O
N
C2H5
R3
SeCH3
4 a: R3 = C2H5
b: R3 = CH2CH2N(C2H5)2
OCH3
CO2H
NH2
5
HNO2, Na2Se2
Na2S2O4
ClCH2COOH
OCH3
CO2H
SeCH2CO2H
6
Ac2O, NaOAc
OCH3
OCOCH3
Se
7
HCl
OCH3
O
Se
8
(C6H5)3P=CHCON(CH3)2
OCH3
R
Se
9 a: R = CH2CON(CH3)2
b: R = CH2CH2N(CH3)2
C2H5S-, DMF
OH
CH2CH2N(CH3)2
Se
1 a: X = NH
b: X = S
c: X = Se

Scheme 1

eliminating the solvent(s) in vacuum. Recrystallizations were realized in E40 (petroleum ether 40-60); E60 (petroleum ether 60-80); T (toluene); TA (toluene-ethanol); AA (ethanol, acetic acid); A.EtOAc (ethanol-ethyl acetate); Ace (acetone). Chromatographic separations were realized on SiO_2 (Macherey Nagel 81533). Ir spectra (KBr 1%) are in cm^{-1}. ^1H Nmr spectra ($CDCl_3$) are in ppm (δ) or Hz (J) and were determined at 400 MHz (unless otherwise stated). ^{13}C Nmr shifts (100 MHz, $CDCl_3$) (broad-band decoupling) are in ppm (δ) with respect to HMDSO (hexamethyldisiloxane). ^{13}C Values were attributed on the basis of values of (*1*)benzoselenophene derivatives.[17] ^{77}Se Nmr shifts (76 MHz, $CDCl_3$) are given in ppm (δ) with respect to CH_3SeCH_3 as external standard. They are compared with ^{77}Se of (*1*)benzoselenophene at 526 ppm.[18] Low resolution mass spectra are given in m/z for the most abundant natural isotopes (^{80}Se, ^{79}Br).

2-Methoxy-6-methylselenobenzaldehyde (2a) : To a solution of *m*-methylselenoanisole [12] (5 g, 0.025 mol) in 20 ml of dry THF, BuLi (0.03 mol) is added dropwise at room temperature and under argon. After stirring for 1 h at the same temperature, the mixture is quenched by DMF (0.03 mol, 2.2 g., 2.3 ml). After stirring the mixture one more hour, the oily residue of the usual work-up is distilled (150-180°C/10mmHg). After recrystallization (E60-80) the distillate affords 0.6 g (10 %) of yellowish needles (mp 98°C); ir $\nu_{C=O}$: 1695. ^1H Nmr 2.1 (s, Se-CH_3, J $^{77}SeCH_3$ = 15); 4.0 (s, OCH_3); 6.7 (d, H_5,J_{5-4} = 8); 6.8 (d, H_3,J_{3-4} = 8); 7.4 (dd, J_{3-4} = 8, J_{4-5} = 8, H_4); 11.0 (s, CHO). Anal. Calcd for $C_9H_{10}O_2Se$: C, 47.1; H, 4.4. Found : C, 46.9; H, 4.4. EIms, m/z : 230 (M^+).

2-Methoxy-6-methylselenobenzoic acid (2b) :

a) From *m*-Methylselenoanisole : The experimental conditions are the same as above but the reaction mixture is poured onto dry ice. After the usual work-up, the solid acid is recrystallized twice (T) giving 0.43 g (7 %) of white plates; (mp 128-130°C); ir ($\nu_{C=O}$) = 1680. ^1H Nmr (60 MHz)

: 10.0 (s, OH); 7.4-6.7 (m, $H_{3,4,5}$); 4.0 (s, OCH_3); 2.1 (s, $SeCH_3$, J $^{77}SeCH_3$ = 16). Anal. Calcd for $C_9H_{10}O_3Se$: C, 44.10; H, 4.08. Found : C, 44.3; H, 4.1.

b) From benzamide **4b** : *o*-Anisic acid (15.2 g, 0.1 mol) is transformed ($SOCl_2$, 50 ml, 0.67 mol) into the corresponding acid chloride. After elimination of the excess of reagent, the crude product is dissolved in CH_2Cl_2 (20 ml) and added dropwise at 5°C to a two phases mixture of 17.3 g (0.12 mol, 21.6 ml) of triethylethylenediamine, 80 ml of 1 M NaOH and 100 ml of CH_2Cl_2. After usual purification a colorless oil is obtained (25.1 g; 90 %) by distillation (174-178°C/10mmHg). EIms, m/z : 278 (M^+). To a cold (-78°C) solution in 100 ml of dry THF of s-BuLi in hexane (17 ml, 0.022 mol) and containing TMEDA (3.3 ml, 0.022 mol), a solution of the preceeding amide (5.6 g, 0.020 mol) in 30 ml of THF is added dropwise. After 2 h at - 78°C, dimethyldiselenide (4.1 g, 2.1 ml, 0.022 mol) is added. The mixture is still stirred for 2 h at - 78°C and then allowed to come to room temperature. After the usual work-up, the amide (**4b**) is purified roughly and submitted to hydrolysis (MeI, NaOEt, HCl).[12] An acid identical with **2b** is obtained in a yield of 10 %.

2-Methoxy-4-methylselenoacetophenone : To a cold (0°C) solution of *m*-methylselenoanisole (15.4 g, 0.07 mol) and acetic anhydride (8.2 g, 7.5 ml, 0.08 mol) in CH_2Cl_2 (100 ml), $AlCl_3$ (21.6 g, 0.16 mol) is added portionwise. Stirring is maintained for 4 h at the same temperature. After the usual work-up the residue is distilled (125-130°C/8mmHg). After recrystallization (E60), the distillate affords 0.34 g (2 %) of yellowish needles (mp 79-80°C). ^1H Nmr (60 MHz) : 2.1 (s, $SeCH_3$; J $^{77}SeCH_3$ = 15); 2.4 (s, $COCH_3$); 3.6 (s, OCH_3); 6.6 (d, J_{5-6} = 8.6, H_5); 6.8 (s, H_3); 7.6 (d, J_{5-6} = 8.6, H_6). Anal. Calcd for $C_{10}H_{12}O_2Se$: C, 49.38; H, 4.93. Found: C, 49.5; H, 5.2.

2-Carboxy-4-methoxybenzo[*b*]selenophene (3a) : A mixture of 9.5 g (0.041 mol) of aldehyde (**2a**) and 5.7 g (0.041 mol) of bromoacetic acid is warmed at 150°C. A fusion and a solidification occur successively. The

solid residue is dissolved in pyridine (10 ml) and acetic anhydride (50 ml). After refluxing for 30 min, the reagents are eliminated in vacuum and the acid is isolated. The residue is taken in 10 % $NaHCO_3$ decolorized with Norit and acidified with conc. HCl. After recrystallization (TA), microcrystals (3.1 g, 30 %) of acid (3a) are isolated (mp 243-245°C). ^1H Nmr (CD_3OD, 60 MHz) : 3.9 (s, OCH_3); 6.8 (d, J_{5-6} = 9, H_5); 7.3 (dd, J_{5-6} = 9, J_{6-7} = 8, H_6); 7.5 (d, J_{6-7} = 8, H_7); 8.2 (s, H_3). Anal. Calcd for $C_{10}H_8O_3Se$: C, 47.0; H, 3.10. Found : C, 47.2; H, 3.2.

4-Methoxybenzo[*b*]selenophene (3b) : Acid (3a) (2.55 g, 0.01 mol) is dissolved in 50 ml of freshly distilled quinoline and boiled (4 h) in the presence of 0.3 g of copper chromite. After elimination of the solvent, the ether (3b) is distilled (120-130°C/1mmHg) and recrystallized (E60). White plates (mp 70°C) are obtained (0.210 g, 10 %). ^1H Nmr (60 MHz) [19] : 3.9 (s, OCH_3); 6.5 (d, J_{5-6} = 7, H_5); 7.1 (dd J_{5-6} = 7. J_{6-7} = 8, H_6); 7.4 (d,J_{6-7} = 8, H_7); 7.6-7.7 (AB system, J_{2-3} = 6, H_2,H_3).

2-Methoxy-6-methylseleno-N-diethylbenzamide (4a) : To a solution of 2-methoxy-*N*-diethylbenzamide (20.7 g, 0.1 mol) in dry THF (25 ml), are added 13.9 g (18 ml, 0.12 mol) of TMEDA and 92.3 ml (0.12 mol) of s-BuLi at - 78°C over 20 min under nitrogen. Dimethyldiselenide (22.6 g, 11.4 ml, 0.12 mol) in 10 ml of THF is then introduced dropwise. The reaction mixture is allowed to come to room temperature and stirred for 1 h.
After the usual work-up the oily residue is distilled (190°C/2mmHg). After recrystallization (E40) it was obtained 6.4 g (32 %) of yellow crystals (mp 62-64°C). Ir $\nu_{C=O}$: 1640. ^1H Nmr(60 MHz) : 2.3 (s, $SeCH_3$; J $^{77}SeCH_3$ = 15); 1.1 (t, J = 12, CH_3CH_2); 3.1 (q, J = 12, CH_2CH_3); 6.6-7.3 (m, H_{3-5}). EIms, m/z : 300 (M^+).

2-Carboxy-3-methoxyphenylselenoacetic acid (6) : 6-Methoxyanthranilic acid [13,14] (5g, 0.03 mol) is dissolved in 25 ml of 6 M HCl. To this cooled (5°C < temperature < 10°C) solution, $NaNO_2$ (2.1 g, 0.03 mol) in

15 ml of water is added dropwise. The so obtained diazonium salt is added dropwise with vigorous stirring to a solution of Na_2Se_2 (prepared from 2.9 g of NaOH, 30 ml of H_2O, 3.1 g of Se and 3.1 g of rongalite). After 1 h, Norit is added and the basic solution is filtered. After acidification with conc. HCl, the crude product is filtered, washed with water and oven dried. 5.1 g (74 %) of a cream-powder are obtained (mp 242-247°C, EIms, m/z : 462 (M^+)) which coloured red on standing. This diselenide (5 g, 0.011 mol) is dissolved in 50 ml of 4 M NaOH and added of 10 g of anhydrous Na_2CO_3. The solution is warmed to 70°C and 6 g of $Na_2S_2O_4$ are introduced ($9 < pH < 10$ by 2M NaOH). The mixture is refluxed for 1 h, cooled to 60°C, added of a neutral aqueous solution of chloroacetic acid (9.5 g, 0.1 mol) and refluxed for 2 h. After cooling, concentrated HCl is added till pH 1; the precipitate is collected and washed with water. After recrystallization (AA), the diacid (6) (mp 195°C) is obtained (5.55 g, 64 % from 6-methoxyanthranilic acid);
ir $\nu_{C=O}$ = 1700, 1720; ^1H nmr (CF_3CO_2H) : 3.3 (s, CH_2, $J^{77}Se-CH_2$ = 12.5); OCH_3 (s, 2.43); 6.5-7.2 (m, $H_{4,5,6}$). EIms, m/z : 290 (M^+).

4-Methoxyselenoindoxylacetate (7) : A mixture of diacid 6 (7 g, 0.024 mol), 50 ml (0.49 mol) of acetic anhydride and 10 g of dry sodium acetate is refluxed for 2 h. After elimination of the reagents and usual work-up, the solid residue is purified by liquid chromatography (eluent: ether/toluene; 1/4). After recrystallization (TE.60), it is obtained 5 g (77 %) of the acetate (7) (mp 135°C). Ir $\nu_{C=O}$: 1755. ^1H Nmr : 2.2 (s, $COCH_3$); 3.8 (s,OCH_3); 6.7 (dd, J_{5-6} = 8; J_{5-7} = 1.4, H_5); 7.08 (dd, J_{5-6} = 8; J_{6-7} = 8, H_6); 7.27 (s, H_2); 7.35 (dd, J_{5-7} = 1.4; J_{6-7} = 8, H_7). ^{77}Se Nmr : 453. ^{13}C Nmr : 20.8 ($COCH_3$); 55.8 (OCH_3); 106.1 (C_2); 113.4 (C_5); 118.9 (C_7); 123.4 (C_{3a}), 126.3 (C_6); 140.5 ($C_{4\ (7a)}$), 142.9 ($C_{7a\ (4)}$), 156.3 (C_3), 169.8 (C=O); EIms, m/z : 270 (M^+).

4-Methoxyselenoindoxyl (8) : Acetate(7)(3.6 g, 0.013 mol) in 200 ml of ethanol containing 25 ml of conc. HCl is refluxed under nitrogen for

3 h. After elimination of the solvent and usual work-up, the selenoindoxyl (8) is purified by crystallization (T.E60). It is obtained 2.5 g (85 %) of pinkish needles (mp 100°C). Ir : $\nu_{C=O}$: 1675. ^{1}H Nmr : 3.8 (s, CH_2, J ^{77}Se-CH_2 = 13.5); 3.9 (s, OCH_3); 6.65 (dd, J_{5-6} = 8, J_{5-7} = 1.3, H_5); 7.0 (dd, J_{6-7} = 8, J_{5-7} = 1.3, H_7); 7.35 (t, J_{5-6} = 8; J_{6-7} = 8, H_6). ^{77}Se Nmr : 307. ^{13}C Nmr : 32.6 (C_2); 55.8 (OCH_3); 107.7 (C_5); 119.8 (C_7); 120.7 (C_{3a}); 136.6 (C_6); 150.2 (C_{7a}); 161,5 (C_4); 199.6 (C=O). EIms, m/z : 228 (M^+).

Dimethylcarbamoylmethylenetriphenylphosphorane : A solution of triphenylphosphine (21 g, 0,08 mol) and *N*,*N*-dimethylchloroacetamide (10 g, 8,5 ml, 0.083 mol) in 150 ml of dry ether is refluxed for 2 h. After cooling the solid is filtered and air dried. White crystals (mp 222°C) are obtained (24.5 g, 80 %). EIms, m/z : 348 (M^+). This phosphonium salt (14.2 g, 0.05 mol) is suspended in 100 ml of water and 200 ml of $CHCl_3$. After dropwise addition of 50 ml of 5 % NaOH, the mixture is vigorously stirred for 2 h. After decantation and elimination of the solvent, the solid is recrystallized (A.EtOAc). The phosphorane is isolated (11.3 g, 65 %) as white microcrystals (mp 172°C). EIms, m/z : 347 (M^+).

4-Methoxy-3-benzo[*b*]selenienyl-*N*,*N*-dimethylacetamide (9a) : The preceeding phosphorane (7 g, 0.02 mol) and selenoindoxyl (8) (4 g, 0.017 mol) are refluxed in 120 ml of dry toluene for 24 h under nitrogen. After elimination of the solvent, the residue is recrystallized (T). The amide (9a) is obtained (2.5 g). Evaporation of the mother liquors leaves a viscous residue which is purified by liquid chromatography (eluent EtOAc : T. 9/1) to give an additionnal crop of 9a. The total yield is 4.2 g (83 %) of pinkish crystals (mp 155°C). ^{1}H Nmr : 2.9 (s, $N(CH_3)_2$); 3.7 (s, OCH_3); 3.9 (s, CH_2); 6.65 (dd, J_{5-6} = 8.2, J_{5-7} = 1.3, H_5); 7.05 (t, J=O, H_6); 7.35 (dd, J_{6-7} = 8.2, J=O, H_7); 7.4 (s, H_2). ^{77}Se Nmr : 506. ^{13}C Nmr : 40.1 (CH_2 and N-CH_3); 57.1 (OCH_3); 107.6 (C_5); 120.4 (C_7); 125.4 ($C_{2(6)}$); 127.0 ($C_{6\ (2)}$); 132.3 (C_{7a}); 135.3 (C_3);145.6 (3a); 159.4 (C_4); 172.9 (C=O). EIms, m/z : 297 (M^+).

3-Dimethylaminoethyl-4-methoxybenzo[*b*]selenophene (**9b**) : To a suspension of $LiAlH_4$ (0.76 g, 0.02 mol) in dry THF (50 ml), a solution of amide (**9a**) (2.96 g, 0.01 mol) in 20 ml of dry THF is added dropwise. The mixture is refluxed for 1 h, cooled (0°C) and hydrolyzed successively with 1 ml of H_2O, 1 ml of 15 % NaOH and 3 ml of H_2O. After filtration of the salts, the cake is washed with THF and the organic phases are dried and evaporated under vacuum. The oily residue is pure enough for the next reaction. ^1H Nmr : 2.2 (s, $N(CH_3)_2$); 2.5 (t, CH_2); 3.05 (t, CH_2N); 3.7 (s, OCH_3); 6.55 (dd, J_{5-6} = 8, J_{5-7} = 1.5, H_5); 7.05 (t, J_{6-7} = 8, J_{5-6} = 8, H_6); 7.25 (dd, J_{6-7} = 8, J_{5-7} = 1.5, H_7); 7.3 (s, H_2). ^{13}C Nmr: 31.4 ($N-CH_3$); 45.1 ($ArCH_2$); 54.7 (OCH_3); 60.4 (CH_2N); 105.2 (C_5); 118.4 (C_7); 122.5 ($C_{2\ (6)}$);125.0 ($C_{6\ (2)}$); 130.1 (C_{3a}); 138.3 (C_{7a}); 144.0. (C_3); 157.3 (C_4). EIms, m/z : 283 (M^+).

3-Dimethylaminoethyl-4-hydroxybenzo[*b*]selenophene : Selenopsilocine (**1c**) To a suspension of NaH (0.54 g, 0.012 mol) in 25 ml of dry DMF, ethanethiol (0.78 g, 0.012 mol, 1 ml) is added at 0°C under nitrogen and vigorous stirring. After 1 h a solution of the amine (**9b**) (1.41 g, 0.005 mol) in 10 ml of dry DMF is added all at once and the reaction mixture is refluxed for 1 h. The solvent is removed under vacuum and the residue is diluted with water. The pH is adjusted to 7 with conc. HCl and the solid is filtered. After recrystallization (Ace-Norit), selenopsilocine (mp 150°C) is obtained (1.02 g, 76 %) and fully characterized.

^1H Nmr : 2.26 (s, $N(CH_3)_2$); 2.70 (t, J = 6.8, $Ar-CH_2$); 3.15 (t, J = 6.8, CH_2-N); 6.73 (d, J_{5-6} = 7.8, H_5); 7.04 (dd, J_{5-6} = 7.8, J_{6-7} = 7.6, H_6); 7.38 (d, J_{6-7} = 7.6, H_7); 7.55 (s, H_2); 12 (s, OH). ^{13}C Nmr : 30.9 ($N-CH_3$); 44.6 ($ArCH_2$); 60.6 ($N-CH_2$); 111.7 (C_5); 117.2 (C_7); 122.5 ($C_{6(2)}$); 125.4 ($C_{2(6)}$); 129.8 (C_{3a}); 137.9 (C_{7a}); 142.8 (C_3); 154.1 (C_4). ^{77}Se Nmr: 497. Anal. Calcd for $C_{12}H_{15}NOSe$: C, 53.53; H, 5.57; N, 5.20. Found: C,53.7; H,5.7;N,5.4.EIms, m/z: 269 (M^+); 225 ($M^+ - N(CH_3)_2$); 211 ($M^+ - CH_2N(CH_3)_2$).

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