SYNTHESIS OF DIBENZO[*d,f*]-1,2-SELENA AND -1,2-THIAZEPIN-3-ONES DERIVATIVES, BIS-HOMOEBSELEN

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Abstract - Dibenzo[*d,f*]-1,2-selena and -1,2-thiazepin-3-ones derivatives were prepared from the corresponding 2-alkylselanyl- and 2-alkylsulfanylbiphenyl-2'-carboxamides or their diselenide or disulfide derivatives. These new seven-membered seleno-compounds are homologues of Ebselen (PZ51) (**1**) which exhibits glutathion peroxidase activity. Bis-homologues of PZ25 (**2**) were also synthesized. Synthesis of benzo[*c*]selenocoumarin *via* a directed ortho metalation-boronic acid cross-coupling reaction and it's ring-opening reaction are the first step of the synthetic pathway.
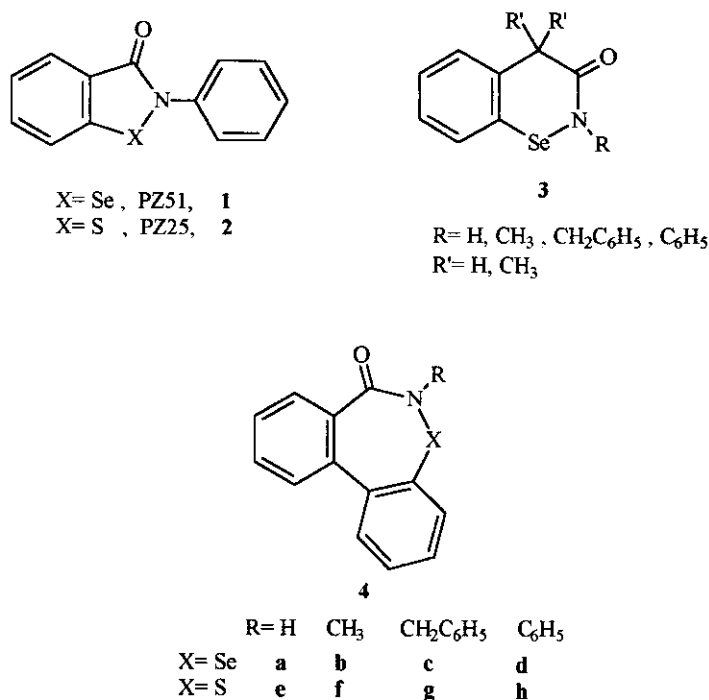
INTRODUCTION

Glutathion peroxidase (GSH-PX) is an important enzyme which catalyses the reduction of a wide variety of hydroperoxides. It is responsible for much of the role of selenium in biology.[1] This selenium-containing enzyme, composed of four sub-units each of which contains one atom of selenium in the form of selenocysteine, participate in a catalytic redox cycle with glutathion. The mechanism of the catalytic reduction has been shown to involve a seleninic acid as the key intermediate.[2]

The synthesis of selenated organic compounds exhibiting GSH-PX-like activity has led to a series of

substances, of which *N*-phenyl-1,2-benzoisoselenazolin-3-one, Ebselen (**1**) (PZ51),[3] has been mostly studied and is presently being investigated in clinical trials. Nevertheless, its poor solubility and its low liposolubility remain a problem for optimal therapeutic development. In order to enhance its solubility and to decrease its compactness,[4] research has been directed towards the more fundamental modification of the Ebselen structure. With this aim, a supplementary tetrahedral carbon group was introduced in the heterocycle in order to break the planar structure leading to 2*H*-3,4-dihydro-1,2-benzoselenazin-3-one (**3**) derivatives [5] which are six-membered homologues of Ebselen keeping the Se-N bond essential for the pharmacological activity.

In the same context, we develop here a synthesis of new dibenzo[*d,f*]-1,2-selena- and -1,2-thiazepin-3-ones (**4**) whose *N*-phenyl derivative is the bis-homoebselen (Scheme 1). The seven-membered heterocycle is


X= Se , PZ51, **1**
X= S , PZ25, **2**

3

R= H, CH$_3$, CH$_2$C$_6$H$_5$, C$_6$H$_5$
R'= H, CH$_3$

4

R=	H	CH$_3$	CH$_2$C$_6$H$_5$	C$_6$H$_5$
X= Se	a	b	c	d
X= S	e	f	g	h

Scheme 1

condensed to a biphenyl framework with respect to three rules. First, the new structure must preserve the Se-C$_{aromatic}$ bond to avoid selenium atom bioavailability which determines the toxicity of seleno-organic compounds. Secondly, we have to keep the Se-N bond responsible of GSH-PX like activity. The third rule

is the presence of nitrogen-carbonyl bond stabilizing the selenenamide structure.

Among the few references in the literature assigned to selena and thiazepinone systems, only one describes

a synthesis of particular dibenzo[d,f]-1,2-thiazepin-3-one derivatives.[6] Benzo[c]thiocoumarin (6) and

benzo[c]selenocoumarin (7) were the milestones which we selected for the synthesis of heptagonal

heterocycles (4). Compound (6) is easily synthesized by cleavage of the sulfur-carbon bond of

dibenzothiophene with lithium, followed by carboxylation with carbon dioxide, as described by Gilman.[7]

Attempts to apply this methodology to dibenzoselenophene failed to give the selenolactone (7). Oxygen

analogue of 6 and 7, dibenzo[b,d]pyran-6-one (5) (Scheme 2), benzo[c]coumarin, is an important skeleton

of biologically and pharmacologically interesting compounds. A large number of synthetic pathways have

been reported for its preparation.[8,9]
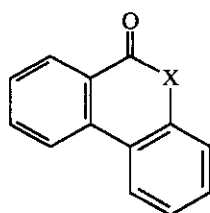
X= O 5
   S 6
   Se 7

Scheme 2

We describe here a synthetic route to benzo[c]selenocoumarin, based on a practical and efficient method

for the construction of the biphenyl framework *via* a directed orthometalation-boronic acid cross-coupling

reaction (Scheme 3). Ring-opening of this new selenolactone and its sulfur analogue in alkali medium or

with amines leads to 2-alkylselanyl- and 2-alkylsulfanylbiphenyl-2'-carboxylic acids, disulfide and

diselenide acids or amides, which are the precursors of the seven-membered compounds (4).

RESULTS AND DISCUSSION

Synthesis of benzo[c]selenocoumarin (7). Orthometalation of benzamide (8) under the Beak's

conditions[10] (s-BuLi/ TMEDA/ THF/ -78°C) followed by trimethyl borate quenching and acidic work-up

gives the crude arylboronic acid (9), which was used directly in the cross-coupling reaction with 2-bromoacetanilide (10) under the Suzuki conditions[11] (toluene/ aqueous Na_2CO_3/ Pd[PPh$_3$]$_4$/ reflux) to give N,N-diisopropyl 2-N'-acetylaminobiphenyl-2'-carboxamide (12). Hydrolysis of acetamide group in a refluxing HCl (6N) solution leads to N,N-diisopropyl 2-aminobiphenyl-2'-carboxamide (16) in 40% yield. Phenanthridinone (13) was formed as by-product and precipitates from the reaction mixture (mp: 290°C, lit.,[12] 291-293°C).
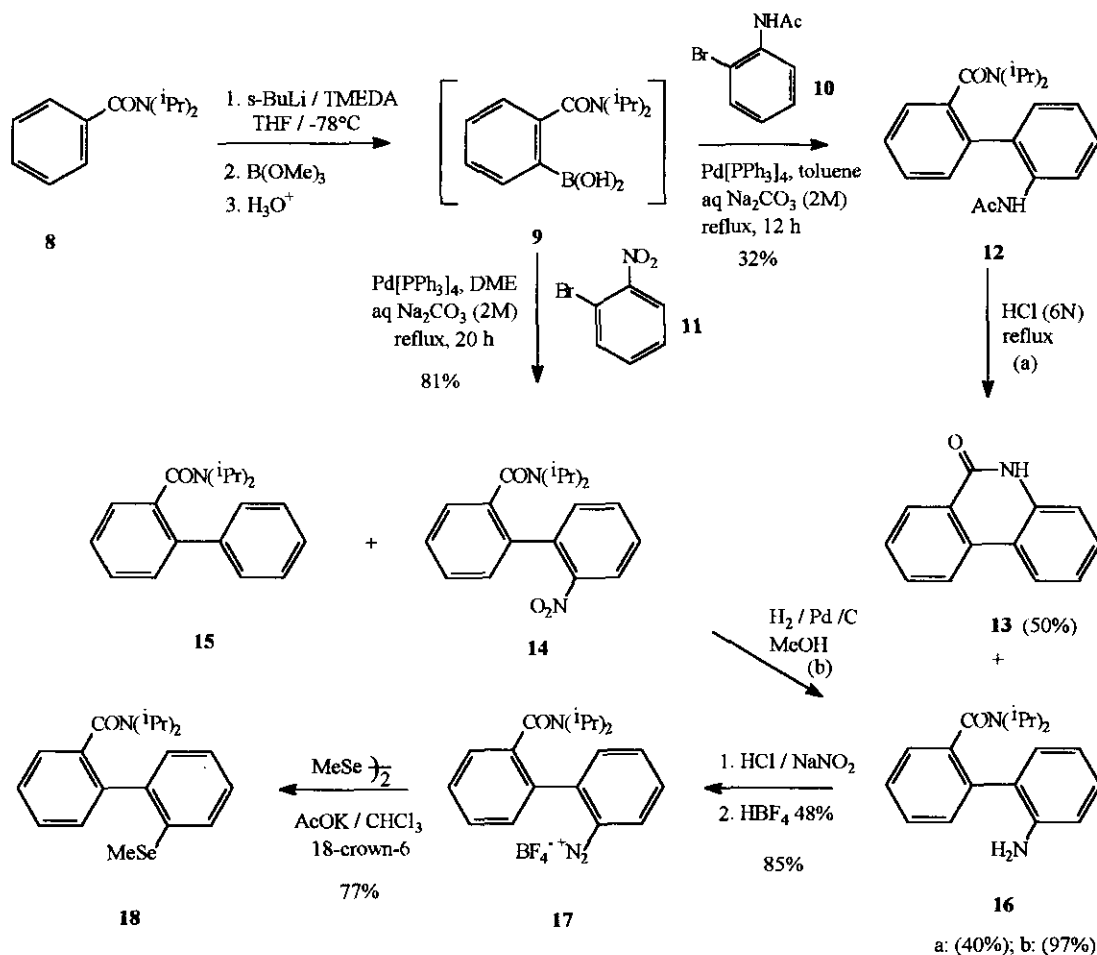
Scheme 3

Thus, we tried to improve the yield of 16 by changing the coupling partner and 2-bromonitrobenzene (11) was chosen. Following the modified Suzuki cross-coupling conditions[13] (DME/ aqueous Na_2CO_3/ Pd[PPh$_3$]$_4$/ reflux) we obtained the biaryl derivative (14) in a good yield. A trace of by-product was

identified as *N,N*-diisopropylbiphenyl-2-carboxamide (**15**). The presence of this product is in agreement

with literature.[14] It results from an exchange with a phenyl group of the catalyst ligand triphenylphosphine

and the intermediate of aryl halide-catalyst oxidative addition. Catalytic hydrogenation of the nitro group

(MeOH/ Pd/C) leads quantitatively to amine (**16**) which upon diazotization by sodium nitrite in HCl

medium at 0< T< 5°C gives arenediazonium tetrafluoroborate (**17**). Radical methylselanyl-

dediazoniation[15] by a phase transfer catalytic reaction of dimethyl diselenide with arenediazonium

tetrafluoroborate (**17**) affords efficiently *N,N*-diisopropyl-2-methylselanylbiphenyl-2'-carboxamide (**18**).

This product was then allowed to cyclize through a convenient method developed in our laboratory
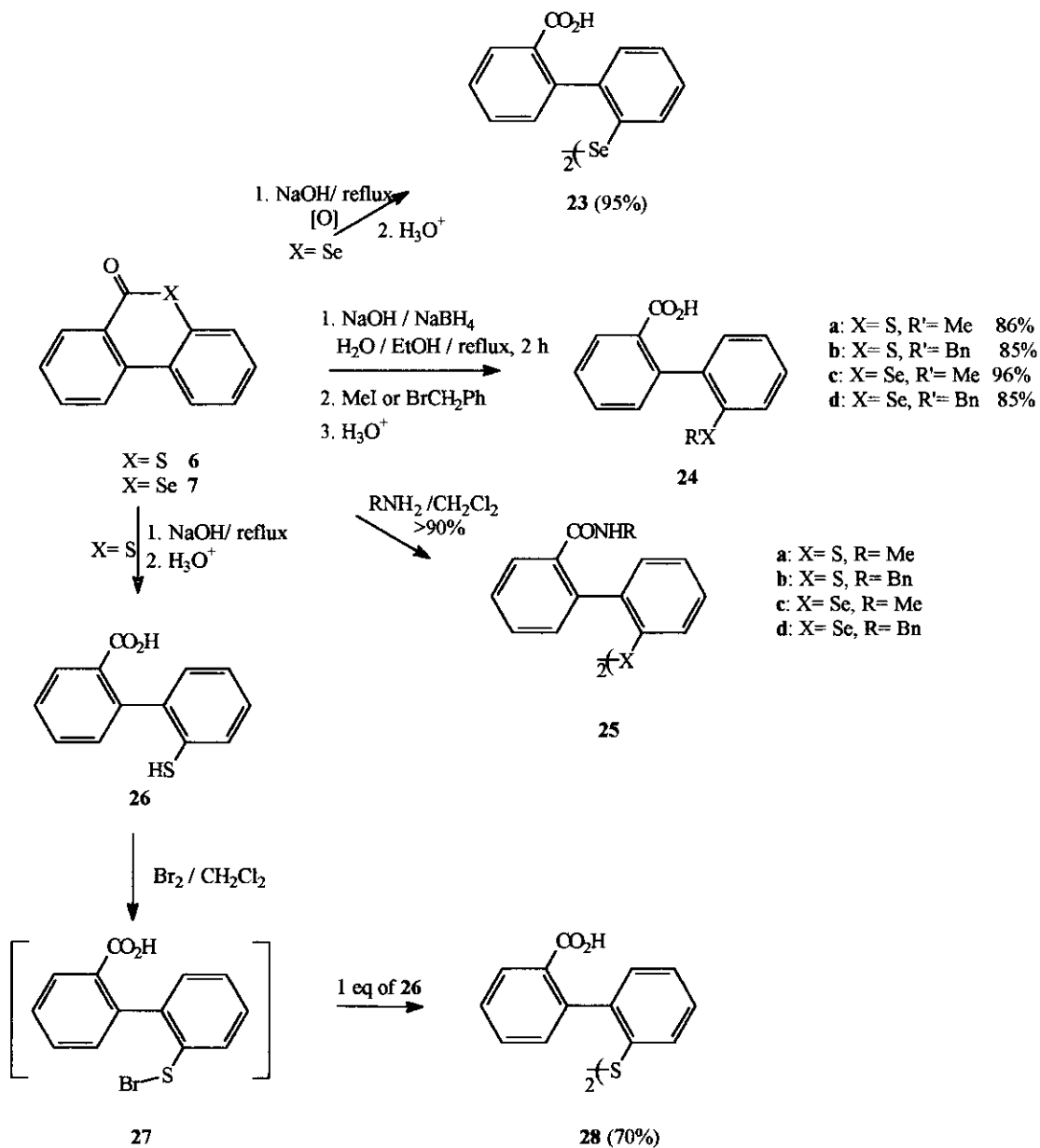
(Scheme 4).
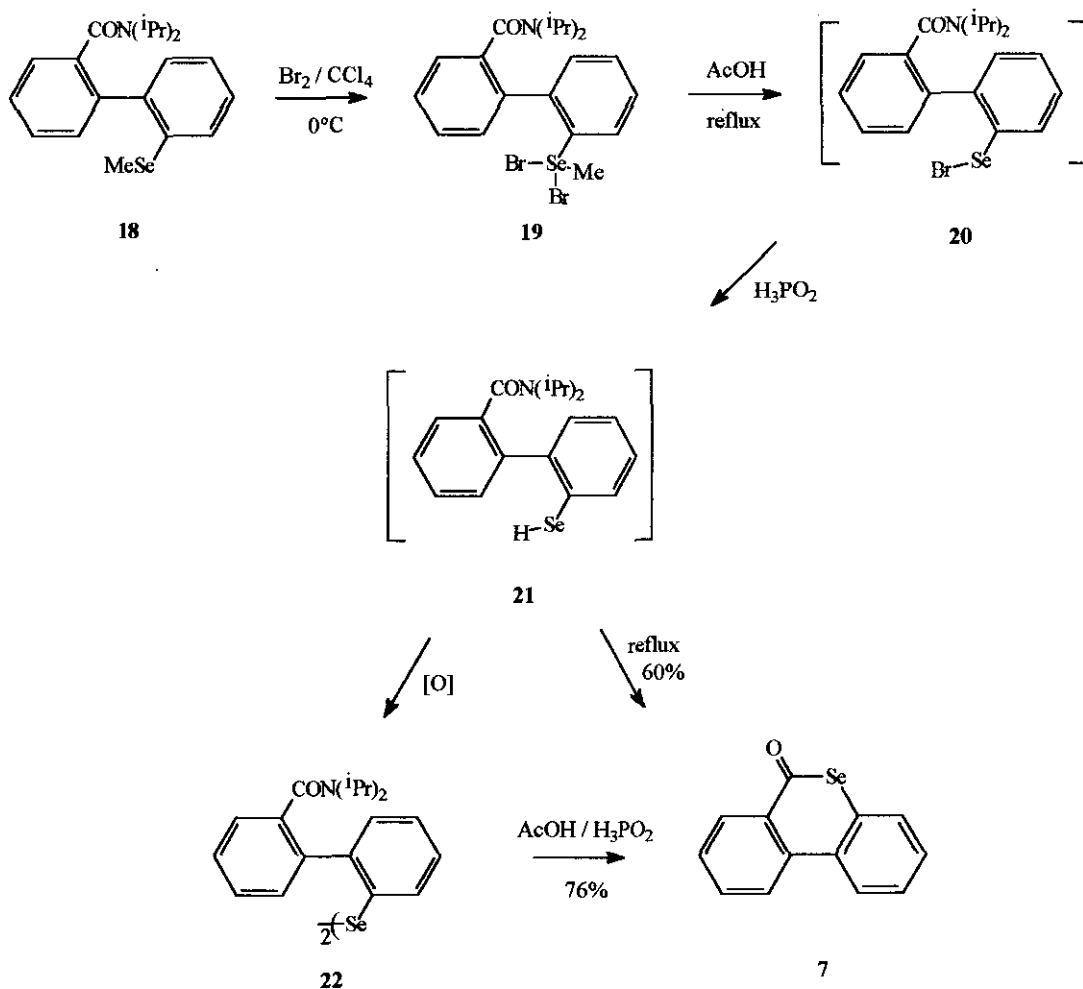
Scheme 4

It involves the quaternization of selenium with bromine leading to the selenonium derivative (**19**). Debromomethylation in refluxing acetic acid affords selenenyl bromide intermediate (**20**). The cyclization is realized by the inversion of polarity obtained through reducing **20** with hypophosphorous acid in refluxing acetic acid. Selenolactone (**7**) is obtained in 60% yield with diselenide (**22**) resulting from the oxidation of the selenol (**21**) during the work-up. The refluxing of **22** in a AcOH-H$_3$PO$_2$ mixture (1:1) also gives **7** in good yield.
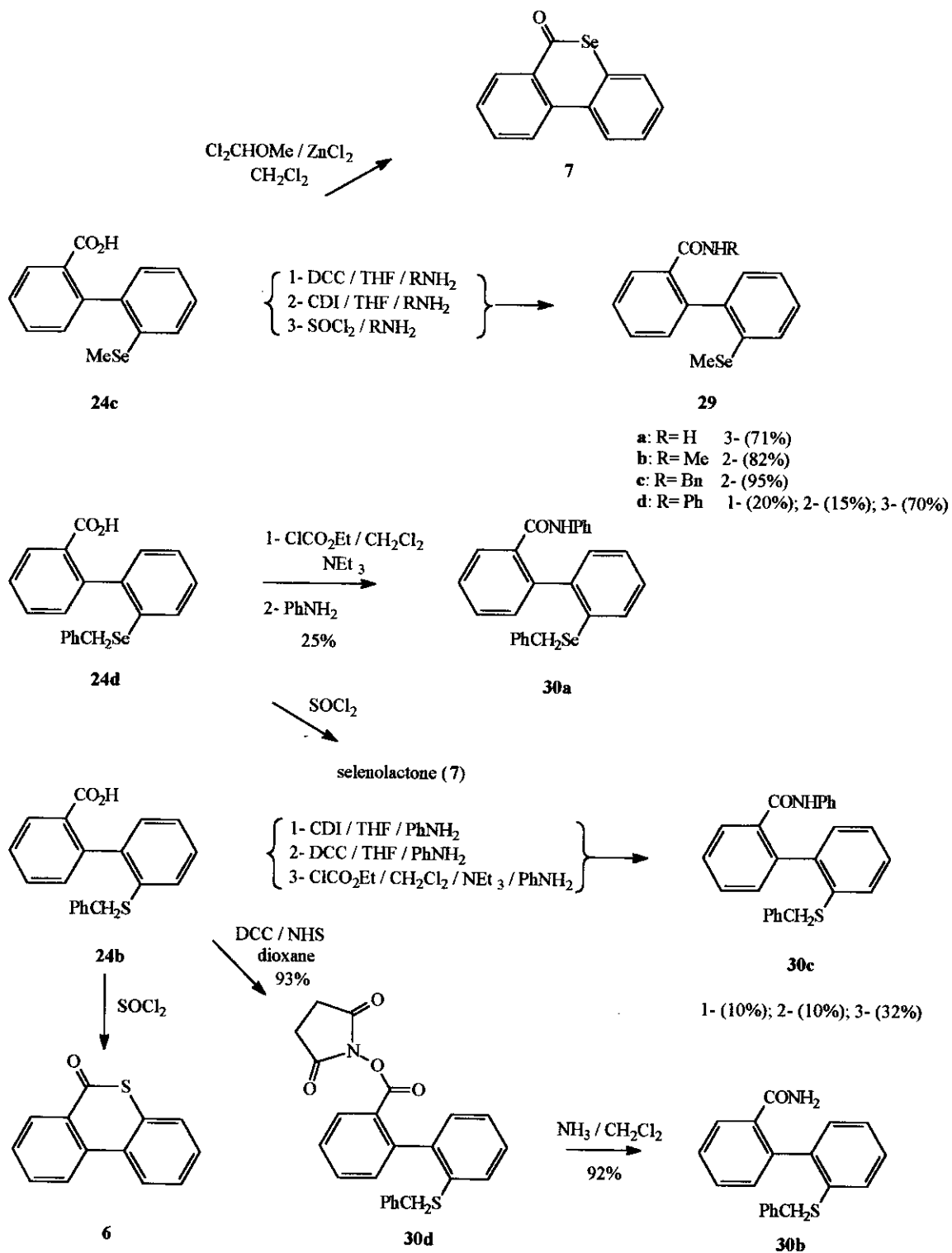
Heterocycles-opening of 6 and 7. Benzo[*c*]selenocoumarin (**7**) and its sulfur analogue (**6**) were hydrolyzed in an alkaline solution to provide, after alkylation, 2-alkylchalcogenobiphenyl-2'-carboxylic acids (**24a-d**) (Scheme 5). Treatment of these heterocycles with an excess of methylamine or benzylamine in CH$_2$Cl$_2$ affords the corresponding diselenide and disulfide areneamides (**25a-d**), while aniline failed to react even after its activation by one equivalent of n-butyllithium in THF. Without reducing agent, selenolactone was hydrolyzed and oxidized by air to 2-biphenyl-2'-carboxylic diselenide acid (**23**). This route was not efficient for preparation of **28**, therefore bromine was used in an alternative method as shown in Scheme 5. Thus, 2-mercaptobiphenyl-2'-carboxylic acid (**26**) was converted into sulfenyl bromide derivative (**27**) by addition of bromine in CH$_2$Cl$_2$ at 0°C. The action of another molecule of thiol (**26**) affords the disulfide acid (**28**).

Synthesis of amides (29a-d) and (30a-c). 2-Methylselanylbiphenyl-2'-carboxylic acid (**24c**) was transformed into corresponding amide (**29a-d**) by treatment with SOCl$_2$, CDI (carbonyldiimidazole) or DCC (*N,N*'-dicyclohexylcarbodiimide) and reaction with ammonia and primary amines (methylamine, benzylamine and aniline) in THF or in CH$_2$Cl$_2$ (Scheme 6). Use of α,α-dichloromethyl methyl ether as activating agent with ZnCl$_2$ as catalyst, in CH$_2$Cl$_2$ gave normally[16] benzo[*c*]selenocoumarin as the major product. Amide (**30a**) was obtained *via* activation of acid (**24d**) with ethyl chloroformate and Et$_3$N in CH$_2$Cl$_2$ followed by treatment with aniline. Selenolactone was obtained with SOCl$_2$. The same result was observed with acid (**24b**) giving benzo[*c*]thiocoumarin as major product. The treatment of acid (**24b**) either by CDI or DCC/ aniline system afforded amide (**30c**) in low yield and only ethyl chloroformate as activating reagent gave a fair yield. Intermediate (**30d**), isolated after treatment of acid (**24b**) with DCC

and NHS (*N*-hydroxysuccinimide) gave amide (**30b**) by ammonolysis in CH_2Cl_2.

CO_2H

23 (95%)

1. NaOH/ reflux
[O]
2. H_3O^+
X= Se

X= S   **6**
X= Se **7**

1. NaOH / NaBH₄
   H_2O / EtOH / reflux, 2 h
2. MeI or BrCH₂Ph
3. H_3O^+

CO_2H

24

a: X= S, R'= Me   86%
b: X= S, R'= Bn   85%
c: X= Se, R'= Me 96%
d: X= Se, R'= Bn 85%

X= S
1. NaOH/ reflux
2. H_3O^+

RNH_2 /CH_2Cl_2
>90%

CONHR

25

a: X= S, R= Me
b: X= S, R= Bn
c: X= Se, R= Me
d: X= Se, R= Bn

CO_2H

HS
26

Br_2 / CH_2Cl_2

CO_2H

Br—S
27

1 eq of **26**

CO_2H

S
28 (70%)

Scheme 5

Cl$_2$CHOMe / ZnCl$_2$
CH$_2$Cl$_2$

7

24c

1- DCC / THF / RNH$_2$
2- CDI / THF / RNH$_2$
3- SOCl$_2$ / RNH$_2$

29

a: R= H   3- (71%)
b: R= Me   2- (82%)
c: R= Bn   2- (95%)
d: R= Ph   1- (20%); 2- (15%); 3- (70%)

24d

1- ClCO$_2$Et / CH$_2$Cl$_2$
NEt$_3$
2- PhNH$_2$
25%

30a

SOCl$_2$

selenolactone (7)

24b

1- CDI / THF / PhNH$_2$
2- DCC / THF / PhNH$_2$
3- ClCO$_2$Et / CH$_2$Cl$_2$ / NEt$_3$ / PhNH$_2$

30c

1- (10%); 2- (10%); 3- (32%)

DCC / NHS
dioxane
93%

SOCl$_2$

6

30d

NH$_3$ / CH$_2$Cl$_2$
92%

30b

Scheme 6

According to the synthesis of benzisoselenazolinone and benzoselenazinone derivatives, a seven-membered ring would be obtained by cyclization of appropriate sulfenyl and selenenyl halides which are generally generated by treatment of the corresponding disulfides or diselenides with Cl$_2$, Br$_2$, SO$_2$Cl$_2$ or SOCl$_2$[17] (Scheme 7; path(a)). Selenenyl bromides are also obtained by the action of bromine on alkylaryl selenides (Scheme 7; path(b)). The presence of a base is often required for the heterocycle formation.
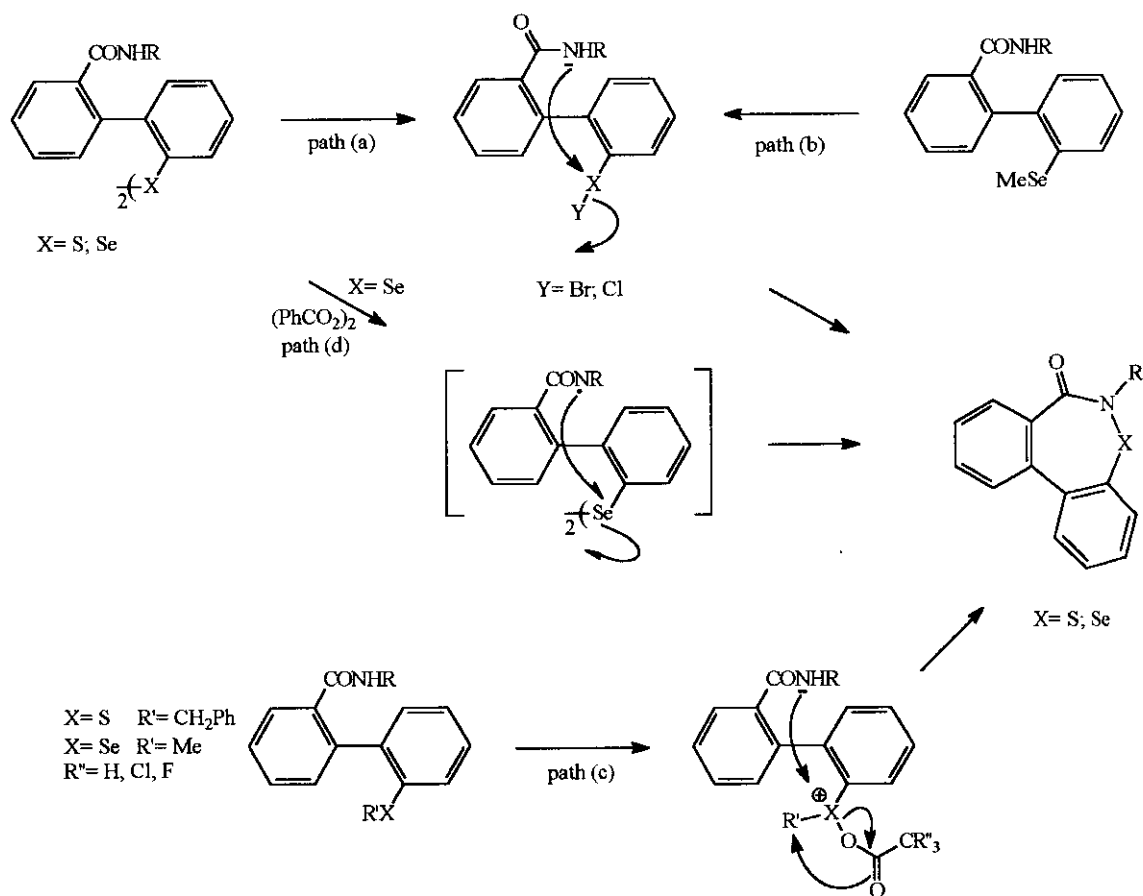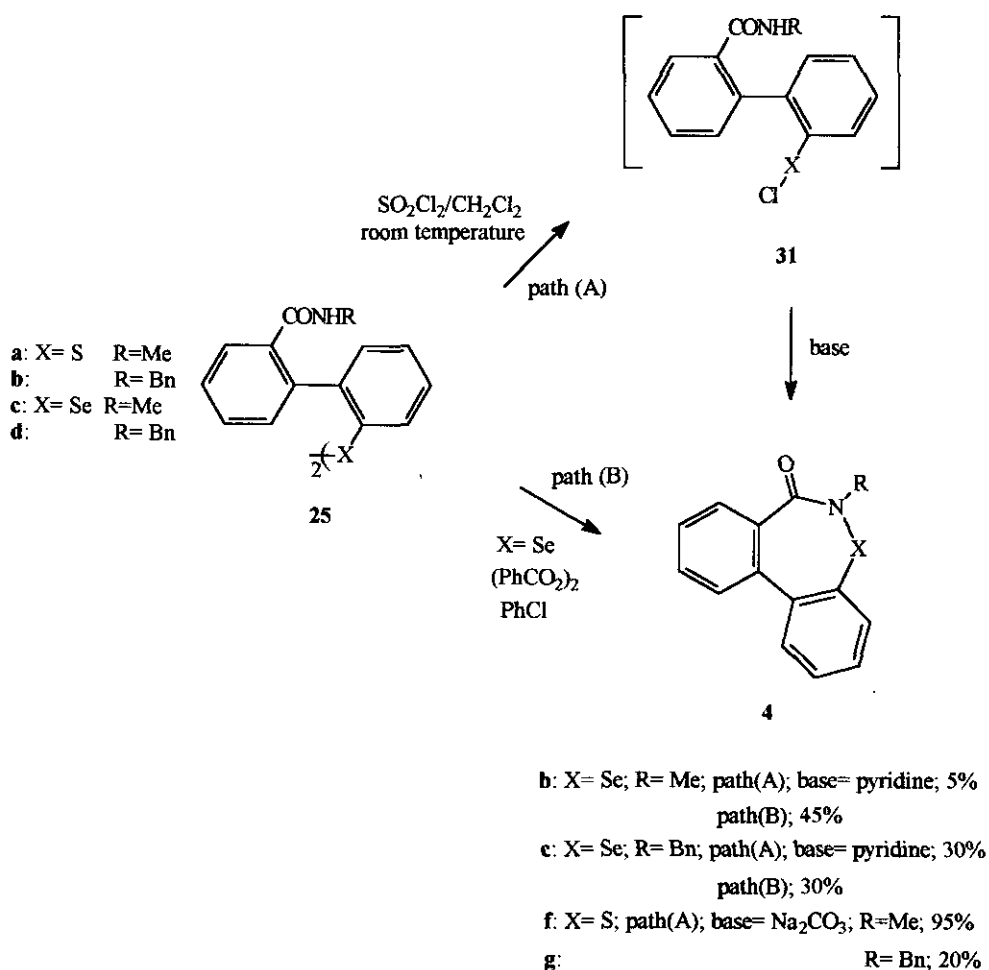

Scheme 7

The cyclization of benzyl sulfoxides and methyl or benzyl selenoxides has also been effective[18] (Scheme 7; path (c)). In fact it's the reaction of acetyl chloride, acetic, trifluoroacetic or trichloroacetic anhydrides with these oxides which provided nitrogen-chalcogen bond formation. These oxides are generally prepared by oxidation of corresponding sulfides or selenides with H$_2$O$_2$ or m-chloroperbenzoic acid (m-CPBA). Recently[19] a new construction of Ebselen under intramolecular homolytic substitution via amidyl radical

intermediate at the selenium atom was reported (Scheme 7; path(d)).

Heterocyclization of disulfide and diselenide amides. Disulfide amides (**25a,b**) (Scheme 8) react with an equivalent of sulfuryl chloride in CH_2Cl_2 leading to the corresponding sulfenyl chlorides (**31a,b**) which were treated with an excess of anhydrous Na_2CO_3 to afford dibenzo[d,f]-1,2-thiazepin-3-ones (**4f,g**). Treatment of diselenides amides (**25c,d**) with the same reagent and refluxing in pyridine gave dibenzo[d,f]-1,2-selenazepin-3-ones (**4b,c**) in low yield. The use of Na_2CO_3 was not effective and regenerated the starting materials. **4b,c** were also obtained by intramolecular radical cyclization of diselenides (**25c,d**) with benzoyl peroxide in chlorobenzene at room temperature.

a: X= S   R=Me
b: R= Bn
c: X= Se   R=Me
d: R= Bn

SO_2Cl_2/CH_2Cl_2
room temperature
path (A)

path (B)
X= Se
$(PhCO_2)_2$
PhCl

base

b: X= Se; R= Me; path(A); base= pyridine; 5%
                 path(B); 45%
c: X= Se; R= Bn; path(A); base= pyridine; 30%
                 path(B); 30%
f: X= S; path(A); base= Na_2CO_3; R=Me; 95%
g: R= Bn; 20%

Scheme 8

Heterocyclization of sulfide and selenide amides. The treatment of amides (**29a-d**) with bromine at 0°C

gave a yellow solid resulting from the quaternization of selenium. Debromomethylation occurs in refluxing dry toluene or chloroform, and gives selenenyl bromides (34e-h) which were cyclized without further purification by addition of an excess of anhydrous Na_2CO_3 to afford new heterocycles (4a-d) (Scheme 9). We have not been able to isolate bis-homoebselen[20] owing to its high instability and its transformation into diselenide (25f). Formation of the cyclized product was confirmed[21] by treatment with thiophenol, in toluene at room temperature, which provided selenosulfide derivative (35). Oxidation pathway of amides (29a-d) and (30a) via selenoxide derivatives (32a-e) was not effective and provided only traces of cyclized products. However this methodology has allowed the synthesis of dibenzo[d,f]-1,2-thiazepin-3-one (4e) via a benzyl sulfoxide derivative (32f) and treatment with trichloroacetic acid. Oxidation of amide (30c) with one equivalent of m-chloroperbenzoic acid followed by action of acetyl chloride provides disulfide (25e) which is probably the consequence of sulfur-nitrogen bond instability in the cyclized product.

Cleavage of the diselenide bond by $SOCl_2$ is known to lead to the corresponding selenenyl chloride. Thus acid (23) was treated with thionyl chloride to give crude 2-chloroselenobiphenyl-2'-carboxylic acid (36), which on treatment with benzylamine affords cyclized product (4c) (Scheme 10). Use of aniline led to the formation of diselenide (25f), corroborating the lability of bis-homoebselen (4d). The process is not the same with the disulfide bond, and acid (28) undergoes reaction with $SOCl_2$ and methylamine or benzylamine to give a mixture of disulfide amides (25a,b), thiolactone (6) and cyclized product (4f,g). Use of aniline gave a mixture of thiolactone and disulfide (25e). Formation of compounds (4f,g) involves cyclization and disproportionation of disulfide amides (25a,b). This method was reported[17a] and is promoted by the presence of a base, such as the amine as shown in Scheme 10. The disulfide amide releases the thiazepinone derivative, and thiol intermediate (37). Upon oxidation, 37 provides starting disulfide amide and benzo[c]thiocoumarin (6) via thiolactonization process. Here, the absence of the sulfur analogue of bis-homoebselen agrees also with its high instability. The corresponding disulfide was the major isolated product. Pharmacological properties of diselenide (25f) are actually under inverstigation.
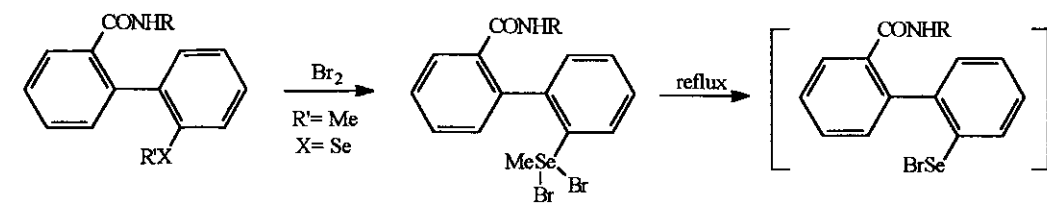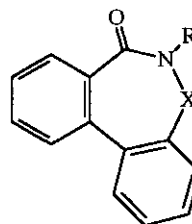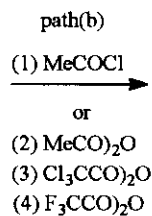
29 **a**: X= Se; R'= Me; R= H
    b: R= Me
    c: R= Bn
    d: R= Ph

30 **a**: X= Se; R'=Bn; R= Ph
    b: X= S;   R'= Bn; R= H
    c: X= S;   R'= Bn; R= Ph

34

e: R= H
f: R= Me
g: R= Bn
h: R= Ph
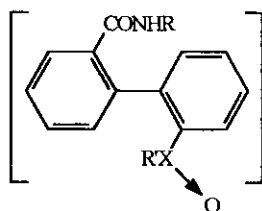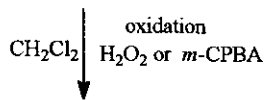
a: R'=Me; X= Se; R= H
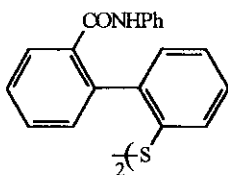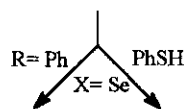**b**:   R= Me
c: R= Bn
d: R= Ph

e: R'= Bn; X= Se; R= Ph
f: R'= Bn; X= S; R= H
g: R= Ph

32

4

a: X= Se; R= H   path(a) (71%)
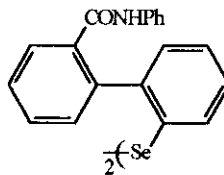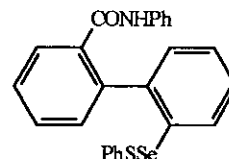**b**:   R= Me   path(a) (50%)
c: R= Bn   path(a) (42%)
d: R= Ph   path (a) (42%)*
e: X= S;   R= H   path(b)(3)(20%)
h: R= Ph   path(b)(1)(23%)*

25e

25f

35

( )* yield of disulphide (**25e**) and diselenide (**25f**)

Scheme 9
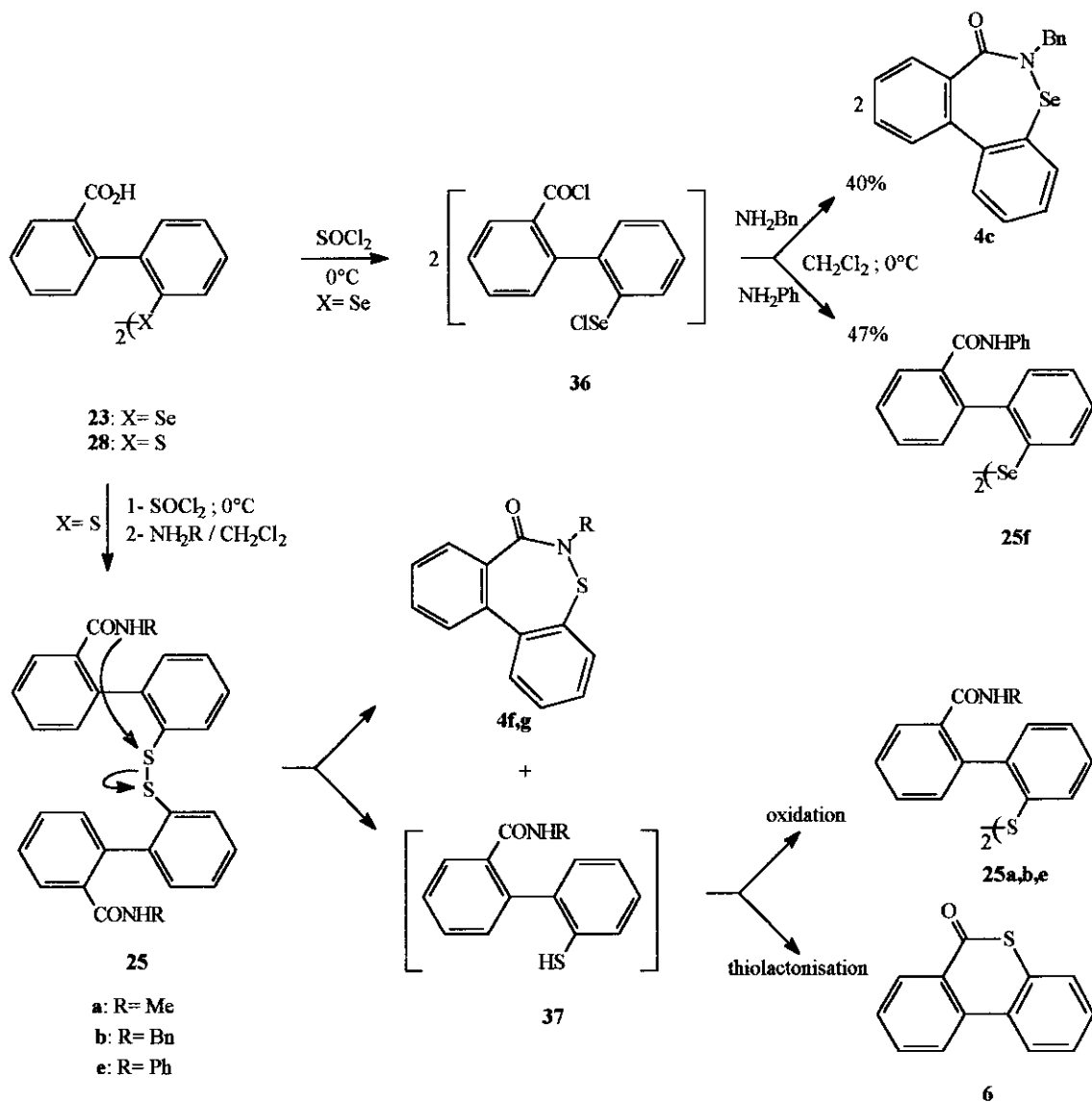
Scheme 10

yield of:	thiazepinone;	disulphide;	thiolactone (6)
R= Me	4f (25%)	25a (60%)	(12%)
R= Bn	4g (15%)	25b (60%)	(23%)
R= Ph	4h (0%)	25e (70%)	(17%)

EXPERIMENTAL

General Procedures. Unless otherwise stated, reactions were carried out in commercial pure grade solvents without further purification. THF was freshly distilled from sodium and potassium. Inorganic

salts, 10% Pd/C catalyst, s-BuLi, diisopropylamine, *N,N,N',N'*-tetramethylethylenediamine, trimethyl borate were purchased from Acros Chimica. Dimethyl diselenide[22] and tetrakis(triphenylphosphine)-palladium Pd[PPh$_3$]$_4$ catalyst[23] were prepared according to literature procedures and stored under nitrogen in a refrigerator (CAUTION: dimethyl diselenide has unpleasant odour). 33% Methylamine in absolute ethanol (8.03M) was purchased from Fluka Chemika, benzylamine, SOCl$_2$, SO$_2$Cl$_2$, Br$_2$, CDI (carbonyldiimidazole), DCC (dicyclohexylcarbodiimide) and *N*-hydroxysuccinimide were purchased from Acros Chimica, aniline was distilled before use and gaseous ammonia bubbling was realized through potassium hydroxide pellets. *N,N*-Diisopropylbenzamide (**8**) was prepared according to standard procedure and purified by recrystallization (mp 68-71°C) (ether-hexane) lit.,[24] mp 69-71°C. 2-Bromoacetanilide (**10**) was prepared by refluxing 2-bromoaniline in an acetic acid- acetic anhydride mixture and purified by recrystallization: mp 92°C (toluene). Analytical tlc was done with silica plates (POLYGRAM SIL G/UV$_{254}$; Macherey-Nagel) and 70-230 mesh silica gel (Macherey-Nagel) was used for column chromatography. Melting points were determined with a Kofler hotplate melting point apparatus and are uncorrected. Nmr spectra were recorded on a Brucker AM 400 instrument, ^{1}H nmr spectra (in CDCl$_3$) δ (ppm) are referenced to HMDSO and coupling constants, *J*, are in Hertz. ^{13}C Nmr spectra are referenced to CDCl$_3$. ^{77}Se chemical shifts are relative to dimethyl selenide as internal standard. Mass spectra were recorded by direct introduction under 70eV. Only isotope ^{80}Se is considered. Elemental analysis were performed by the Institute of Pharmacy (Liege, Belgium). Ir spectra were recorded on a Perkin Elmer 1600 series FTIR spectrophotometer and were measured as KBr discs or liquid films.

N,N-Diisopropyl-2-acetylaminobiphenyl-2'-carboxamide (12). A solution of s-BuLi (30.7 ml, 43 mmol of a 1.4 M solution in hexane) was added dropwise to a mixture of *N,N*-diisopropylbenzamide (**8**) (8 g, 39 mmol) and TMEDA (6.5 ml, 43 mmol) in anhydrous THF (150 ml) at -78°C under nitrogen. The mixture was stirred for 1 h at this temperature and treated with B(OMe)$_3$ (5.5 ml, 48 mmol) in THF (30 ml). The solution was then allowed to warm to ambient temperature, acidified with 5% HCl solution and stirred for 1 h. The organic phase was dried on MgSO$_4$, filtered and evaporated. The green oil obtained was allowed to react with 2-bromoacetanilide (**10**) (8.30 g, 39 mmol), Pd[PPh$_3$]$_4$ (1.30 g, 1.2 mmol) in toluene (150 ml)

and Na$_2$CO$_3$ (8.30 g, 78 mmol) in water (39 ml). The mixture was refluxed for 12 h and evaporated to dryness and the residue was extracted with CH$_2$Cl$_2$ (150 ml) and filtered. The filtrate was dried on MgSO$_4$, filtered and evaporated to yield an oil which crystallized. Recrystallization in toluene-petroleum ether (40°-60°) affords 4.22 g (32%) of cross-coupling compound: mp 130°C; ^{1}H nmr (CDCl$_3$) δ 1.90 (s, 3H, CH$_3$ (Ac)), 0.66 (d, 3H, J= 7.1 Hz, CH$_3$ (^{i}Pr)), 0.93 (d, 6H, J= 7.0 Hz, CH$_3$ (^{i}Pr)), 1.40 (d, 3H, J= 7.1 Hz, CH$_3$ (^{i}Pr)), 3.16 (septet, 1H, J= 7.1 Hz, CH (^{i}Pr)), 3.50 (septet, 1H, J= 7.0 Hz, CH (^{i}Pr)), 9.00 (m, 1H, NH), 6.83-8.00 (m, 8H, ArH); ms (m/z):338 (M$^+$).

N,N-Diisopropyl-2-nitrobiphenyl-2'-carboxamide (14). To a solution of N,N-diisopropylbenzamide **(8)** (50 g, 244 mmol), TMEDA (39 ml, 268 mmol) in anhydrous THF (850 ml) at -78°C under nitrogen was added dropwise a solution of s-BuLi (206 ml, 268 mmol, of 1.3 M solution in hexane-cyclohexane mixture). After stirring for 1 h at -78°C, the mixture was treated with B(OMe)$_3$ (83 ml, 732 mmol), allowed to warm to room temperature over 15 h, cooled to 0°C and acidified to pH 6-6.5 with 5% aqueous HCl. Removal of THF in vacuo followed by treatment of the residual oil with water (700 ml), extraction with CH$_2$Cl$_2$, washing the organic extract with saturated brine solution, drying on MgSO$_4$, filtration, and evaporation to dryness in vacuo provided a green oil which on chromatographic analysis by tlc (eluent: toluene-acetone (80:20)) showed no starting benzamide.

To a suspension of Pd[PPh$_3$]$_4$ (5.70 g, 4.90 mmol) in anhydrous DME (700 ml) was added 2-bromonitrobenzene **(11)** (32.90 g, 163 mmol) and the mixture was stirred for 10 min. To this solution were added sequentially the precedent phenylboronic acid (~1.5 eq) dissolved in a minimum of DME and Na$_2$CO$_3$ (34.60 g, 327 mmol) in water (163 ml, 2M solution). The mixture was refluxed for 15 h, cooled, and filtered. The filtrate was evaporated to dryness and the residue was treated with saturated NaCl solution and extracted with CH$_2$Cl$_2$. Drying the organic extract over MgSO$_4$, filtration and evaporation gave a solid which was recrystallized three times in cyclohexane to give 43 g (80%) of cross-coupling product **(14)**: mp 114°C; ^{1}H nmr (CDCl$_3$) δ 0.56 (d, 3H, J= 6.1 Hz, CH$_3$ (^{i}Pr)), 0.97 (d, 3H, J= 6.1 Hz, CH$_3$ (^{i}Pr)), 1.09 (d, 3H, J= 4.8 Hz, CH$_3$ (^{i}Pr)), 1.46 (d, 3H, J= 6.2 Hz, CH$_3$ (^{i}Pr)), 3.23 (septet, 1H, J= 6.8 Hz, CH (^{i}Pr)), 3.87 (m, 1H, CH (^{i}Pr)), 7.11-7.88 (m, 8H, ArH); ms (m/z): 326 (M$^+$); ir (ν, cm^{-1}): 1622

(C=O).

N,N-Diisopropyl-2-aminobiphenyl-2'-carboxamide (16).

a- Hydrolysis of 12. A suspension of *N,N*-diisopropyl-2-acetylaminobiphenyl-2'-carboxamide (**12**) (1 g, 3 mmol) in 6N HCl (20 ml) was heated till complete dissolution then cooled to room temperature. The phenanthridinone (**13**) was filtered and the filtrate was basified with 5% NaOH solution and extracted with CH_2Cl_2. The organic extract was dried over $MgSO_4$, filtered and the filtrate evaporated. Solid residue was recrystallized in cyclohexane-petroleum ether (60°-80°) mixture to give 0.35 g (40%) of amine (**16**).

b- Reduction of 14. A solution of nitro compound (**14**) (10 g, 31 mmol) in methanol (200 ml), and 10% Pd/C (0.25 g) was stirred under hydrogen pressure (50 psi) for 6 h. After the end of reaction, the mixture was filtered and evaporated to provide a brown oil which crystallizes on standing. Recrystallization in a cyclohexane-petroleum ether (60°-80°) mixture affords 8.8 g (97%) of a white solid: mp 169-170°C; ^{1}H nmr (CDCl$_3$) δ 0.76 (d, 3H, J= 6.1 Hz, CH$_3$ (^{i}Pr)), 0.96 (d, 3H, J= 6.0 Hz, CH$_3$ (^{i}Pr)), 1.09 (d, 3H, J= 6.7 Hz, CH$_3$ (^{i}Pr)), 1.46 (d, 3H, J= 6.6 Hz, CH$_3$ (^{i}Pr)), 3.23 (septet, 1H, J= 6.1 Hz, CH (^{i}Pr)), 3.57 (septet, 1H, J= 6.7 Hz, CH (^{i}Pr)), 3.85 (m, 2H, NH$_2$), 6.66-7.36 (m, 8H, ArH), ms (m/z): 296 (M$^+$); ir (ν, cm^{-1}): 1614 (C=O), 3345 and 3470 (NH).

Arenediazonium tetrafluoroborate (17). Amine (**16**) (11 g, 37 mmol) was added to a solution of 36% HCl (17 ml) and water (17 ml). The mixture was stirred for 10 min at room temperature and then cooled to a temperature between 0°C and 5°C. To this solution was added dropwise, with vigorous stirring, a solution of sodium nitrite (2.56 g, 37 mmol) in water (5.3 ml). After the end of addition, the mixture was rapidly filtered and to the filtrate was added a solution of 48% tetrafluoroboric acid (4.89 g, 10.2 ml, 56 mmol). An oil was separated by addition of a minimum amount of ether. After the solidification and filtration, the solid was washed successively with cold ethanol (10 ml) and ether (10 ml) to give 12.47 g (85%) as a white solid. Structure of diazonium salt (**17**) was confirmed by ms, (m/z) at 299 agrees with fluoro-dediazonation (Schiemann reaction) occurring in the spectrometer.

N,N-Diisopropyl-2-methylselanylbiphenyl-2'-carboxamide (18). To a stirred suspension of the diazonium salt (**17**) (10 g, 25 mmol), 18-crown-6 (0.10 g) and dimethyl diselenide (3.6 ml, 38 mmol) in

CHCl$_3$ (150 ml), was added in the dark and at 0°C, melted and pulverized potassium acetate (4.90 g, 51 mmol). Stirring was continued at ambient temperature for 64 h and the reaction mixture was filtered. The filtrate was washed with water, dried over MgSO$_4$, filtered and concentrated under reduced pressure to give a brown oil as a crude reaction product. Liquid chromatography over silica gel (cyclohexane-ethyl acetate 80:20) gave 7.3 g (77%) of the selenated compound (18): mp 104-108°C; ^{1}H nmr (CDCl$_3$) δ 0.46 (d, 3H, J= 6.5 Hz, CH$_3$ (^{i}Pr)), 0.90 (d, 3H, J= 6.5 Hz, CH$_3$ (^{i}Pr)), 1.08 (d, 3H, J= 6.8 Hz, CH$_3$ (^{i}Pr)), 1.45 (d, 3H, J= 6.8 Hz, CH$_3$ (^{i}Pr)), 3.17 (septet, 1H, J= 6.8 Hz, CH (^{i}Pr)), 3.65 (septet, 1H, J= 6.5 Hz, CH (^{i}Pr)), 2.19 (s, 3H, J^{77}Se-CH$_3$= 11.5 Hz, SeCH$_3$), 7.11-7.48 (m, 8H, ArH), ms (m/z): 375 (M$^+$, 5%), 280 (M-95, 100%); ir (ν, cm^{-1}): 1628 (C=O).

Benzo[c]selenocoumarin (7). To a solution of compound (18) (8 g, 21 mmol) in CH$_2$Cl$_2$ (30 ml) and CCl$_4$ (30 ml) was added bromine (1.2 ml, 24 mmol). The mixture was refluxed under stirring for 2 h and the chlorinated solvents were evaporated in vacuo. To the orange residue of 20 was added acetic acid (30 ml) and hypophosphorous acid (15 ml) and the solution was boiled for 20 h. The reaction mixture was cooled and poured into ice-water (150 ml) and extracted with CH$_2$Cl$_2$. The organic extract was washed with 8.4% NaHCO$_3$ solution, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The solid residue obtained was chromatographied over silica gel (toluene) to provide 3.4 g (60%) of selenolactone (7) as a lightly yellow crystalline solid: mp 113-115°C; ^{1}H nmr (CDCl$_3$) δ 7.29-8.27 (m, 8H, ArH); ^{13}C nmr (CDCl$_3$) δ 185.74 (C=O), 120.85-132.34 (Ar). ^{77}Se nmr (CDCl$_3$) δ 567 (s, 1Se); ms (m/z): 260 (M$^+$, 33%); 232 (M-28, 68%); 180 (M-80, 37%); 152 (M-108, 100%); ir (ν, cm^{-1}): 1643 (C=O); Anal. Calcd for C$_{13}$H$_8$OSe: C, 60.24; H, 3.12. Found: C, 59.92; H, 3.13.

The diselenide (22) (2 g) obtained during the work-up was converted easily to the cyclized product in 76% of yield by refluxing in a AcOH (50 ml)-H$_3$PO$_2$ (5 ml) mixture. For diselenide (22): mp 210°C; ^{1}H nmr (CDCl$_3$) δ 0.44 (s, 3H, CH$_3$ (^{i}Pr)), 0.90 (s, 3H, CH$_3$ (^{i}Pr)), 1.09 (s, 3H, CH$_3$ (^{i}Pr)), 1.45 (s, 3H, CH$_3$ (^{i}Pr)), 3.18 (m, 1H, CH (^{i}Pr)), 3.60 (m, 1H, CH (^{i}Pr)), 7.15-7.80 (m, 8H, ArH); ms (m/z): 718 (M$^+$); ir (ν, cm^{-1}): 1614 (C=O).

2-Methylselanyl and benzylselanylbiphenyl-2'-carboxylics acids (24c,d) and their sulfur analogues

(24a,b). The benzo[*c*]selenocoumarin or benzo[*c*]thiocoumarin opening was carried out by refluxing a mixture of the heterocycle (13 mmol), sodium borohydride (0.49 g, 13 mmol), sodium hydroxide (2.10 g, 52 mmol) in water (30 ml) and ethanol (15 ml) for 2 h and cooled to 0°C. The solution was then treated with alkyl halide (13 mmol) and allowed to warm to room temperature. The ethanol was evaporated in vacuo and the residual basic solution was acidified with 29% HCl to give a precipitate which was filtered and dissolved with a solution of 10.5% Na_2CO_3, treated with charcoal then filtered. The filtrate was acidified with 5% HCl solution, the precipitate formed was filtered, washed with water and dried in air. Recrystallization in toluene-petroleum ether afforded acids (24a) (86%), (24b) (85%), (24c) (96%) and (24d) (85%).

2-Methylthiobiphenyl-2'-carboxylic acid (24a). mp 126-128°C; ^1H nmr ($CDCl_3$) δ 2.28 (s, 3H,CH_3), 7.09-8.05 (m, 8H, ArH); 10.45 (br m, 1H, OH); ^{13}C nmr ($CDCl_3$) δ 10.92 (CH_3), 119.67-136.79 (Ar), 167.24 (C=O); ms (m/z): 244 (M^+); ir (ν, cm^{-1}): 1692 (C=O), 2287-3344 (OH).

2-Benzylthiobiphenyl-2'-carboxylic acid (24b). mp 138-140°C; ^1H nmr ($CDCl_3$) δ 3.83, 3.88 (AB system, 2H, *J*= 12.9 Hz, CH_2), 7.13-8.10 (m, 13H, ArH); 10.79 (br m, 1H, OH), ^{13}C nmr ($CDCl_3$) δ 33.56 (CH_2), 121.04-137.50 (Ar), 166.86 (C=O); ms. (m/z): 320 (M^+); ir (ν, cm^{-1}): 1677 (C=O), 2350-3325 (OH).

2-Methylselanylbiphenyl-2'-carboxylic acid (24c). mp 122-126°C; ^1H nmr ($CDCl_3$) δ 2.14 (s, 3H, J^{77}Se-CH_3= 11.5 Hz, CH_3), 7.10-8.07 (m, 8H, ArH), 11.28 (br m, 1H, OH); ^{13}C nmr ($CDCl_3$) δ 2.04 (CH_3), 120.57-137.91 (Ar), 167.21 (C=O); ms (m/z): 292 (M^+); ir (ν, cm^{-1}): 1679 (C=O), 2250-3301 (OH).

2-Benzylselanylbiphenyl-2'-carboxylique acid (24d). mp 135-137°C; ^1H nmr ($CDCl_3$) δ 3.91, 3.87 (AB system, 2H, *J*= 11.6 Hz, CH_2), 7.09-8.07 (m, 13H, ArH), 11.32 (br m, 1H, OH); ^{13}C ($CDCl_3$) δ 26.49 (CH_2), 121.55-139.06 (Ar), 166.90 (C=O); ms (m/z): 368 (M^+); ir (ν, cm^{-1}): 1676 (C=O), 2359-3378 (OH).

2-Biphenyl-2'-carboxylic acid diselenide (23). A solution of selenolactone (7) (0.10 g, 0.38 mmol) and sodium hydroxide (0.06 g, 1.50 mmol) in water (2 ml) and ethanol (2 ml) was heated with refluxing for 2 h. The yellow mixture was stirred for 15 h in the air and then ethanol was evaporated under reduced pressure. The red basic residual solution was acidified with 5% HCl solution to give a yellow solid which

was extracted with CH_2Cl_2. Organic extract was taken in 10.5% Na_2CO_3 solution (20 ml). The basic phase was treated with charcoal, filtered and acidified with 5% HCl to give, after filtration, 0.1 g (95%) of acid (23) as a yellow crystalline solid: mp 102-108°C; ^1H nmr (CDCl$_3$) δ 7.00-8.10 (m, 9H, ArH, OH); ms (m/z): 552 (M$^+$); ir (ν, cm^{-1}): 1692 (C=O), 2360-3290 (OH).

2-Biphenyl-2'-carboxylic acid disulfide (28):

a- 2-Mercaptobiphenyl-2'-carboxylic acid (26). A solution of thiolactone (6) (0.50 g, 2.36 mmol) and sodium hydroxide (0.38 g, 9.40 mmol) in water (5 ml) and ethanol (5 ml) was heated with refluxing for 2 h then ethanol was evaporated under reduced pressure. The basic residual solution was acidified to give a white solid. Filtration gave 0.32g (60%) of thiol (26): mp 120-121°C; ^1H nmr (CDCl$_3$) δ 7.00-8.40 (m, 10H, ArH, OH, SH); ir (ν, cm^{-1}): 1680 (C=O), 3460-2500 (OH), 2553 (SH).

b- Oxidative coupling. Bromine (0.22 ml, 0.40 mmol) was added to a stirred cold solution of thiol (26) (0.10 g, 0.40 mmol) in CH_2Cl_2 (5 ml). Stirring was continued for 1 h at room temperature. Reaction mixture was cooled and then an other equivalent of thiol (0.10 g, 0.40 mmol) was added. The solution was allowed to warm at room temperature and the CH_2Cl_2 evaporated. The solid residue was purified by the basification (10.5% Na_2CO_3) and acidification (5% HCl) sequences to give 0.14 g (70%) of acid (28) as a white solid: mp 202-212°C; ^1H nmr (CDCl$_3$) δ 7.10-7.90 (m, 9H, ArH, OH)); ms (m/z): 458; ir (ν, cm^{-1}): 1696 (C=O), 3450-2500 (OH).

Diselenide and disulfide amides (25a-d). Thio- or selenolactone (6, 7) were aminolyzed with 3 equivalents of methylamine (33%, 8.03 M solution in absolute ethanol) to affords corresponding disulfide and diselenide amides (25a,c). N-Benzyl analogues (25b,d) were obtained with the use of 3 equivalents of benzylamine in ethanol as opening agent. Absence of starting material by tlc (toluene) was used as a criterion of complete conversion. Recrystallization in cyclohexane yielded pure compounds (25a-d) (>90%).

N-Methyl 2-biphenyl-2'-carboxamide disulfide (25a). mp 65-70°C; ^1H nmr (CDCl$_3$) δ 2.53 (d, 3H, J= 4.7 Hz, CH$_3$), 2.50 (d, 3H, J= 4.8 Hz, CH$_3$), 5.66 (m, 2H, 2NH); 7.10-7.71 (m, 16H, ArH); ^{13}C nmr (CDCl$_3$) δ 26.40 (CH$_3$), 26.42 (CH$_3$), 168.95 (C=O), 126.80-141.35 (Ar); ms (m/z): 484 (M/2);

ir (ν, cm^{-1}): 1646 (C=O), 3284 (NH).

N-Benzyl 2-biphenyl-2'-carboxamide disulfide (25b). mp 60-65°C; ^{1}H nmr (CDCl$_3$) δ 4.10-4.35 (2AB

systems, 4H, 2CH$_2$), 5.73 (m, 1H, NH), 5.78 (m, 1H, NH), 6.75-7.78 (m, 26H, ArH); ^{13}C nmr (CDCl$_3$) δ

43.70 (CH$_2$), 43.80 (CH$_2$), 167.89 (C=O), 126.37-139.14 (Ar); ms (m/z): 634 (M$^+$); ir (ν, cm^{-1}): 1651

(C=O), 3267 (NH).

N-Methyl 2-biphenyl-2'-carboxamide diselenide (25c). mp 73-83°C; ^{1}H nmr (CDCl$_3$): δ 2.49 (d, 3H, J=

3.3 Hz, CH$_3$), 2.51 (d, 3H, J= 3.4 Hz, CH$_3$), 5.55 (m, 2H, NH); 7.10-7.71 (m, 16H, ArH); ^{13}C nmr

(CDCl$_3$) δ 26.42 (CH$_3$), 168.72 (C=O), 126.80-140.70 (Ar); ^{77}Se nmr (CDCl$_3$) δ 412, 413 (d, 2Se); ms

(m/z): 578 (M$^+$); ir (ν, cm^{-1}): 1646 (C=O), 3295 (NH).

N-Benzyl 2-biphenyl-2'-carboxamide diselenide (25d). mp 63°C; ^{1}H nmr (CDCl$_3$) δ 4.11-4.36 (2AB

systems, 4H, 2CH$_2$), 5.78 (m, 1H, NH), 5.83 (m, 1H, NH), 6.75-7.78 (m, 26H, ArH); ^{13}C nmr (CDCl$_3$) δ

43.70 (CH$_2$), 43.80 (CH$_2$), 167.89 (C=O), 126.37-139.14 (Ar); ^{77}Se nmr (CDCl$_3$) δ 412, 414 (d, 2Se); ms

(m/z): 365 (M/2); ir (ν, cm^{-1}): 1634 (C=O), 3251 (NH).

2-Methylselanylbiphenyl-2'-carboxamide (29a). A suspension of acid (**24c**) (0.20 g, 0.68 mmol) and

thionyl chloride (5 ml, 68 mmol) was stirred at 0°C for 30 min then the excess of SOCl$_2$ was eliminated

under reduced pressure. The residual oil was dissolved in CH$_2$Cl$_2$ (10) ml and gaseous ammonia was

passed through the solution during 15 min. The stirring was continued for 30 min at room temperature,

then the reaction mixture was hydrolysed by a 5% HCl solution and extracted with CH$_2$Cl$_2$. Organic

extract was washed with a 10.5% Na$_2$CO$_3$ solution, dried over MgSO$_4$, filtered and evaporated. To the

residual oil were added toluene and silica. After stirring for 5 min, the mixture was filtered and the silica

residue was washed with toluene-ethyl acetate 80:20 mixture then the filtrate was evaporated to afford an

oil which crystallized on standing. Recrystallization in cyclohexane-ethanol mixture gave 0.14 g (71%) of a

white solid: mp 80-86°C; ^{1}H nmr (CDCl$_3$) δ 2.21 (s, 3H, CH$_3$), 5.57 (s, 2H, NH$_2$), 7.15-7.88 (m, 8H,

ArH); ^{13}C nmr (CDCl$_3$) δ 6.32 (CH$_3$), 170.00 (C=O); 125.60-141.00 (Ar); ms (m/z): 293 (M+2);

ir (ν, cm^{-1}): 1667 (C=O); 3132 and 3464 (NH).

N-Phenyl 2-methylselanylbiphenyl-2'-carboxamide (29d). A solution of acid (24c) (0.80 g, 2.70 mmol) in $SOCl_2$ (10 ml, 137 mmol) was stirred for 2 h at 0°C then the excess of $SOCl_2$ was eliminated under vacuum. The residue was dissolved in CH_2Cl_2 (20 ml) and treated with freshly distilled aniline (1.25 ml, 13,70 mmol) at room temperature. After stirring for 45 min, the reaction mixture was hydrolyzed with dilute 5% HCl, extracted with CH_2Cl_2 and the organic extract was washed with 10.5% Na_2CO_3, dried over $MgSO_4$, filtered and evaporated. Purification in silica gel column (toluene as eluent) gave 0.7 g (70%) of pure amide: mp 84-92°C; ^1H nmr ($CDCl_3$) δ 2.25 (s, 3H, $J^{77}SeCH_3$= 11.8 Hz, CH_3), 7.57 (s, 1H, NH); 7.00-7.95 (m, 13H, ArH); ^{13}C nmr ($CDCl_3$) δ 166.41 (C=O), 5.50 (CH_3), 119.60-140.43 (Ar); ms (m/z): 367 (M^+, 1%), 272 (M-95, 100%); ir (v, cm^{-1}): 1649 (C=O), 3236 (NH).

N-Methyl 2-methylselanylbiphenyl-2'-carboxamide (29b). To a mixture of acid (24c) (0.40 g, 1.40 mmol) and CDI (0.24 g, 1.50 mmol) was added dry THF (15 ml) (CO_2 evolution) at room temperature. After stirring for 1 h, methylamine (0.68 ml, 5.50 mmol, 8.03M solution in ethanol) was added and stirring was continued for 2 h. The solvents were evaporated under vacuum and the residual oil was hydrolysed with 5% HCl and extracted with CH_2Cl_2. The organic extract was washed with 10.5% Na_2CO_3 solution, dried over $MgSO_4$, filtered and then evaporated to give an oil which crystallized on standing. Recrystallization in cyclohexane gave 0.34 g (82%) of pure product: mp 86°C; ^1H nmr($CDCl_3$) δ 2.14 (s, 3H, $J^{77}SeCH_3$= 12 Hz, CH_3), 2.52 (d, 3H, J= 4.8 Hz, CH_3), 5.70 (s, 1H, NH), 7.02-7.68 (m, 8H, ArH); ms (m/z): 305 (M^+); ir (v, cm^{-1}): 1633 (C=O), 3261 (NH).

N-Benzyl 2-methylselanylbiphenyl-2'-carboxamide (29c). To a mixture of acid (24c) (0.50 g, 1.71 mmol) and CDI (0.31 g, 1.50 mmol) was added dry THF (15 ml) (CO_2 evolution) at room temperature. After stirring for 1 h, benzylamine (0.37 ml, 3.42 mmol) was added and stirring was continued for 2 h at room temperature. The THF was evaporated under vacuum and the residual oil was hydrolysed with 5% HCl and extracted with CH_2Cl_2. Organic extract was washed with 10.5% Na_2CO_3 solution, dried over $MgSO_4$, filtered and then evaporated to give an oil which crystallized on standing. Recrystallization in cyclohexane gave 0.62 g (95%) of pure white solid: mp 112-116°C; ^1H nmr ($CDCl_3$) δ 1.87 (s, 3H, $J^{77}SeCH_3$ 11.9 Hz, CH_3), 4.07, 4.27 (AB system, 2H, J_{Ha-Hb}= 14.5 Hz, J_{NH-Ha}= 4.5 Hz, J_{NH-Hb}= 6.2, CH_2),

6.07 (s, 1H, NH), 6.68-7.72 (m, 13H, ArH); ms (m/z): 381 (M$^+$); ir (v, cm^{-1}): 1638 (C=O); 3306.8 (NH).

N-Phenyl 2-benzylselanylbiphenyl-2'-carboxamide (30a). To a stirred solution, at room temperature, of acid (**24d**) (1 g, 2.70 mmol) and triethylamine (0.38 ml, 2.70 mmol) in CH$_2$Cl$_2$ (40 ml) was added ethylchloroformate (0.31 ml, 3.26 mmol) and the stirring was continued for 1 h at room temperature. Analyses by tlc in toluene-acetone (8:2) showed the clean formation of a new product and disappearance of starting acid. Reaction mixture was then treated with aniline (0.99 ml, 10.87 mmol) and allowed to reflux for 16 h. The solution was cooled, hydrolysed with 5% HCl solution and extracted with CH$_2$Cl$_2$. The organic extract was washed with 10.5% Na$_2$CO$_3$ solution, dried over MgSO$_4$, filtered and evaporated under reduced pressure. Residual oil was purified upon silica gel column (toluene as eluent) to provide 0.3 g (25%) of green oil: ^{1}H nmr (CDCl$_3$) δ 4.08 (AB system, 2H, CH$_2$); 7.00-7.98 (m, 19H, ArH); ^{13}C nmr (CDCl$_3$) δ 26.67 (CH$_2$), 114.70-138.00 (Ar), 162.27 (C=O).

N-Phenyl 2-benzylthiobiphenyl-2'-carboxamide (30c). To a stirred solution of acid (**24b**) (0.50 g, 1.56 mmol) and Et$_3$N (0.22 ml, 1.56 mmol) in CH$_2$Cl$_2$ (30 ml) was added dropwise, ethyl chloroformate (0.15 ml, 1.56 mmol) in CH$_2$Cl$_2$ (5 ml). After 30 min at room temperature, tlc in toluene-acetone (8:2) showed the clean formation of a new product at the expense of starting acid. The reaction mixture was then treated with aniline (0.28 ml, 3.12 mmol) and the stirring was continued for 16 h at room temperature. The solution was washed successively with a 5% HCl solution and 10.5% Na$_2$CO$_3$ solution, dried over MgSO$_4$, filtered and evaporated under vacuum. Residual oil was purified on silica gel column (toluene as eluent) to afford 0.2 g (32%) of light yellow oil: ^{1}H nmr (CDCl$_3$) δ 4.06 (s, 2H, CH$_2$); 7.00-8.00 (m, 19H, ArH); ^{13}C nmr (CDCl$_3$) δ 32.20 (CH$_2$), 114.70-134.37 (Ar), 161.10 (C=O); ms (m/z): 395 (M$^+$); ir (v, cm^{-1}): 1711 (C=O), 3316 (NH).

2-Benzylthiobiphenyl-2'-carboxamide (30b):

a- N-Hydroxysuccinimidyl 2-benzylthiobiphenyl-2'-carboxylate (30d). DCC (0.39 g, 1.88 mmol) in dry dioxane was added to a solution of acid (**24b**) (0.50 g, 1.56 mmol) and N-hydroxysuccinimide (0.22 g, 1.88 mmol) in dry dioxane (10ml). After stirring during 5 h at room temperature, the precipitate (N,N'-dicyclohexylurea) was filtered and the filtrate evaporated to dryness. The residue was dissolved in CH$_2$Cl$_2$,

washed with 10.5% Na_2CO_3 solution, dried over $MgSO_4$, filtered and concentrated to provide 0.45 g (93%) of light green solid: mp 148-152°C; ^1H nmr ($CDCl_3$) δ 2.71 (s, 4H, 2 CH_2 (succinimidyl)), 3.91 (s, 2H, CH_2); 7.15-8.20 (m, 13H, ArH); ms (m/z): 418 (M+1); ir (ν, cm^{-1}): 1775, 1742 (C=O).

b- Synthesis of amide (30c). Gaseous ammonia was bubbled through a stirred solution of (**30d**) (0.50 g, 1.20 mmol) in CH_2Cl_2 (20 ml) for 5 min at 0°C. The stirring was continued for 2 h then the resulting turbid solution was filtered and the filtrate was evaporated. Purification upon silica gel column with toluene-acetone (9:1) as eluent gave 0.35 g (92%) of pure solid: mp 109-111°C; ^1H nmr ($CDCl_3$) 3.98, 4.03 (AB system, 2H, J= 13 Hz, CH_2); 5.35 (s, 2H, NH_2); 7.15-7.85 (m, 13H, ArH); ^{13}C 37.58 (CH_2), 169.80 (C=O), 125.79-137.85 (Ar); ms (m/z): 319 (M^+); ir (ν, cm^{-1}): 1672 (C=O), 3143 and 3463 (NH).

Dibenzo[d,f]-1,2-selena et thiazepin-3-ones derivatives, general procedures:

a- Cyclisation by Br_2-Na_2CO_3 system. A stirred saturated solution of **29a-d** (5 mmol) in CCl_4 (8 ml) and $CHCl_3$ (2 ml) at 0°C was treated with bromine (0.30 ml, 5.50 mmol) to give an orange precipitate which was filtered and then allowed to reflux in $CHCl_3$ until complete dissolution. The resulting brown solution was cooled to room temperature and treated with an excess of anhydrous Na_2CO_3 (4.20 g, 40 mmol) and the end of reaction was indicated by disappearance of the dark colour. The reaction mixture was then filtered, evaporated and the residual oil was chromatographied upon silica gel column (toluene-ethylacetate (9.5:0.5)) to give the corresponding selenazepinones derivatives (**4a-c**). Instead of **4d** we isolated diselenide (**25f**).

b- Cyclisation by SO_2Cl_2-Na_2CO_3 system. A solution of diselenide and disulfide amides (**25a-d**) (3 mmol) in CH_2Cl_2 (10 ml) at 0°C was treated under stirring with an equivalent of sulfuryl chloride to give a yellow coloured solution. Addition of an excess of Na_2CO_3 allowed the discoloration of the solution which was filtered and concentrated under reduced pressure. Purification upon silica gel column (toluene-ethyl acetate (9.5:0.5)) gave the selena and thiazepinones derivatives (**4b,c,f,g**).

d- Radical cyclisation by $(PhCO_2)_2$. Diselenide amides (**25c,d,f**) (5 mmol) were allowed to react with an equivalent of benzoyl peroxide in chlorobenzene (10 ml) at room temperature. Concentration of the reaction mixture and purification upon silica gel column (toluene-ethyl acetate (9:1)) gave the

selenazepinones (**4b,c**) and (**4d**). This later disproportionate to starting diselenide (**25f**).

e- Cyclisation *via* chalcogen oxidation. Only sulfur amides (**30b,c**) were cyclized by this method with acceptable yields. **30b,c** (5 mmol) were first dissolved in CH$_2$Cl$_2$ (11 ml) at 0°C and reacted with *m*-chloroperbenzoic acid (0.86g, 5 mmol) to form the corresponding sulfoxides (**32f,g**) which were cyclized, without further isolation, with trichloroacetic anhydride or acetylchloride (1.1 equivalent) to thiazepinone (**4e**) and (**4h**) which leads to disulfide amide (**25e**).

N-Methyl dibenzo[*d,f*]-1,2-thiazepin-3-one (**4f**). mp 64°C; ^{1}H nmr (CDCl$_3$) δ 3.29 (s, 3H, CH$_3$); 7.32-7.88 (m, 8H, ArH); ^{13}C nmr (CDCl$_3$) 39.75 (CH$_3$), 127.86-143.69 (Ar), 173.45 (C=O); ms (m/z): 241 (M$^+$, 100%), 226 (M-15, 1.8%), 209 (M-32, 41%), 184 (M-57, 93%), 152 (M-89, 38%); ir (ν, cm^{-1}): 1641 (C=O); Anal. Calcd for C$_{14}$H$_{11}$NOS: C, 69.68; H, 4.59; N, 5.80; S, 13.29. Found: C, 69.73; H, 4.69; N, 5.96; S, 12.95.

N-Benzyl dibenzo[*d,f*]-1,2-thiazepin-3-one (**4g**). mp 114°C; ^{1}H nmr (CDCl$_3$) δ 4.99, 5.03 (AB system, 2H, *J*= 14.4 Hz, CH$_2$), 7.18-7.97 (m, 13H, ArH); ^{13}C nmr (CDCl$_3$) δ 54.97 (CH$_2$), 127.39-143.53 (Ar), 173.44 (C=O); ms (m/z): 317 (M$^+$, 90%), 285 (M-32, 12%); 240 (M-77, 6%), 226 (M-91, 2%), 212 (M-105, 100%), 184 (M-133, 36%); 152 (M-165, 30%); ir (ν, cm^{-1}): 1643 (C=O); Anal. Calcd for C$_{20}$H$_{15}$NOS: C, 75.68; H, 4.76; N, 4.41; S, 10.10. Found: C, 75.71; H, 4.90; N, 4.62; S, 9.91.

N-Methyl dibenzo[*d,f*]-1,2-selenazepin-3-one (**4b**). mp 88-97°C; ^{1}H nmr (CDCl$_3$) δ 3.42 (s, 3H, CH$_3$), 7.24-7.86 (m, 8H, ArH); ^{13}C nmr (CDCl$_3$) δ 41.50 (CH$_3$), 126.30-144.00 (Ar), 173.80 (C=O); ^{77}Se nmr (CDCl$_3$) 874 (s, 1Se); ms (m/z): 289 (M$^+$, 22%), 260 (M-29, 2.4%), 232 (M-57, 94%), 209 (M-80, 100%), 180 (M-109, 68%), 152 (M-137, 96%); ir (ν, cm^{-1}): 1626 (C=O); Anal. Calcd for C$_{14}$H$_{11}$NOSe: C, 58.34; H, 3.85; N, 4.86. Found: C, 58.72; H, 4.09; N, 4.93.

N-Benzyl dibenzo[*d,f*]-1,2-selenazepin-3-one (**4c**). mp 114-121°C; ^{1}H nmr (CDCl$_3$) δ 4.91, 5.06 (AB system, 2H, CH$_2$), 7.19-7.84 (m, 13H, ArH); ^{13}C nmr (CDCl$_3$) δ 55.86 (CH$_2$), 127.25-143.93 (Ar), 173.65 (C=O); ^{77}Se nmr (CDCl$_3$) δ 828 (s, 1Se); ms (m/z): 365 (M$^+$, 1.3%), 285 (M-80, 6%); 260 (M-105, 96%), 232 (M-133, 100%), 180 (M-185, 80%), 152 (M-213, 100%); ir (ν, cm^{-1}): 1627 (C=O); Anal. Calcd for

$C_{20}H_{15}NOSe$: C, 65.94; H, 4.15; N, 3.84. Found: C, 66.15; H, 4.33; N, 3.91.

Dibenzo[d,f]-1,2-thiazepin-3-one (4e). mp 150-155°C; ^{1}H nmr (CDCl$_3$) δ 7.83 (s, 1H, NH), 7.33-7.93 (m, 8H, ArH); ^{13}C nmr (CDCl$_3$) δ 176.24 (C=O), 128.94-144.96 (Ar); ms (m/z): 227 (M$^+$, 100%), 212 (M-15, 11.7%), 195 (M-32, 100%), 184 (M-43, 100%), 152 (M-75, 100%); ir (ν, cm^{-1}): 3132 (NH), 1642 (C=O); Anal. Calcd for $C_{13}H_9NOS$: C, 68.70; H, 3.99; N, 6.16; S, 14.11. Found: C, 68.83; H, 4.05; N, 6.33; S, 13.93.

N-Phenyl 2-biphenyl-2'-carboxamide disulfide (25e). mp 70-74°C, ^{1}H nmr (CDCl$_3$) δ 6.92-7.98 (m, 28H, ArH, NH); ^{13}C nmr (CDCl$_3$) δ 165.51 (C=O), 119.70-137.40 (Ar); ms (m/z): 304 (M/2, 3%), 272 (M/2-32, 100%), 227 (M/2-77, 3%), 212 (M/2-92, 55.3%), 184 (M/2-120, 100%), 152 (M/2-152, 100%); ir (ν, cm^{-1}): 1655 (C=O), 3300 and 3398 (NH); Anal. Calcd for $C_{38}H_{28}N_2O_2S_2$: C, 74.96; H, 4.65; N, 4.6; S, 10.54. Found: C, 74.87; H, 5.02; N, 4.12; S, 10.44.

Dibenzo[d,f]-1,2-selenazepin-3-one (4a). mp 178-188°C; ^{1}H nmr (CDCl$_3$) δ 7.3-7.82 (m, 9H, ArH, NH); ^{13}C nmr (CDCl$_3$) 175.11 (C=O), 127.80-144.50 (Ar); ^{77}Se nmr (CDCl$_3$) δ 741 (s, 1Se); ms (m/z): 275 (M$^+$, 42.4%), 232 (M-43, 77.7%), 195 (M-80, 100%); 180 (M-95, 54.5%), 152 (M-123, 93%); ir (ν,cm^{-1}): 1635 (C=O), 3122 (NH); Anal. Calcd for $C_{13}H_9NOSe$: C, 56.95; H, 3.31; N, 5.11. Found: C, 55.45; H, 3.46; N, 4.92.

N-Phenyl 2-biphenyl-2'-carboxamide diselenide (25f). mp 173-176°C; ^{1}H nmr (CDCl$_3$) δ 6.94-8.00 (m, 28H, ArH, NH); ^{13}C nmr (CDCl$_3$) δ 165.47 (C=O), 119.74-140.03 (Ar); ^{77}Se nmr (CDCl$_3$) δ 398, 406 (d, 2Se); ms (m/z): 352 (M/2, 2.8%), 272 (M/2-80, 6.9%), 232 (M/2-120, 75.7%), 180 (M/2-172, 19%), 152 (M/2-200, 100%); ir (ν,cm^{-1}): 1661 (C=O), 3252, 3284 and 3382 (NH); Anal. Calcd for $C_{38}H_{28}N_2O_2Se_2$: C, 64.96; H, 4.02; N, 3.99. Found: C, 65.49; H, 4.31; N, 4.08.

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20. Isolated product which was a light green coloured oil was different from selenenyl bromide (**34h**) and was characterized only by ^{1}H nmr (δ 7.10-7.90) and gave directly diselenide (**25f**) before complete characterization.

21. Tlc analysis shows transformation of the cyclized product (**4d**) into unknown compound probably seleno sulfide (**35**) which disproportionates to diselenide (**25f**) and diphenyl disulfide (PhSSPh). GC-ms analysis confirms this result.

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