Pergamon

Tetrahedron, Vol. 53, No. 22, pp. 7445-7460, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00454-7

Carbonyl Transposition on Organoselenium Compounds

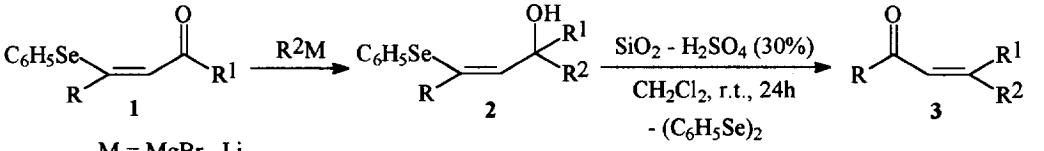
João V. Comasseto,* Wai L. Lo and Nicola Petragnani

Instituto de Química - Universidade de São Paulo, São Paulo, SP - Brazil

Abstract: Carbonyl conjugated vinylic selenides undergo 1,3 and 1,5-carbonyl transposition sequences through organometallic reagents addition reactions followed by acid hydrolysis.

INTRODUCTION

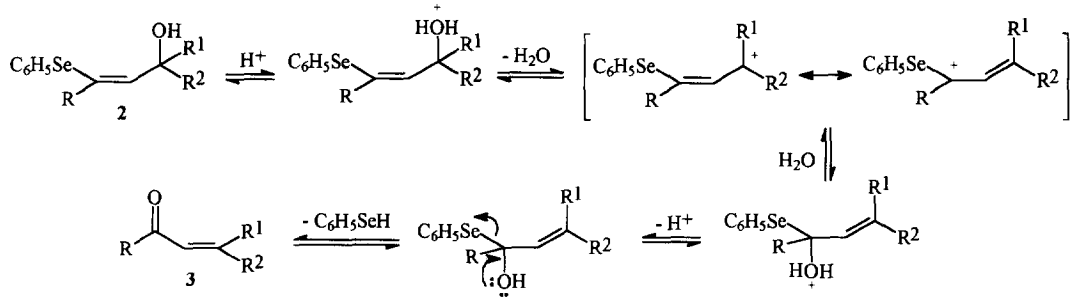
A few years ago we reported that β-phenylseleno-α,β-unsaturated carbonyl compounds are converted into selenium free conjugated enones and enals by a sequence of addition reaction with Grignard or organolithium reagents, followed by acidic treatment of the intermediate allylic alcohol **2**[1] (Scheme 1).



M = MgBr , Li
R = H , alkyl ; R^1 = H , alkyl , OR ; R^2 = alkyl , Ar

Scheme 1

This 1,3-carbonyl transposition sequence[2] can be rationalized as involving the formation of an allylic carbocation, resulted from an acid promoted dehydration of the intermediate allylic alcohol **2**, followed by a trapping of water at the γ position, leading to a mixed allylic phenylseleno hemiketal. Further elimination of a phenylselenol molecule leads to the selenium free α,β-unsaturated carbonyl compound **3** (Scheme 2).



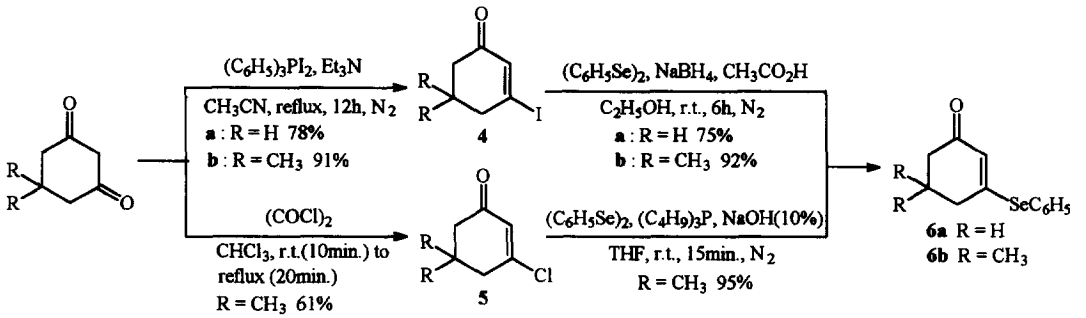
Scheme 2

In spite of the viability of this methodology, it can be foreseen that the high acid concentration (30% H_2SO_4) of the hydrolysis step might be aggressive to substrates more functionalized. In order to optimize both steps of the transposition sequence (Scheme 1) and to establish its scope and limitations, it was undertaken an extensive study involving different organometallic reagents and β-phenylseleno-α,β-unsaturated carbonyl compounds, as well as several hydrolysing systems. Herein we give a full account of our studies and, in addition, show that this sequence is also suitable to perform 1,5-carbonyl transpositions when 5-phenylseleno-2,4-dienoates are used as starting material.

RESULTS AND DISCUSSION

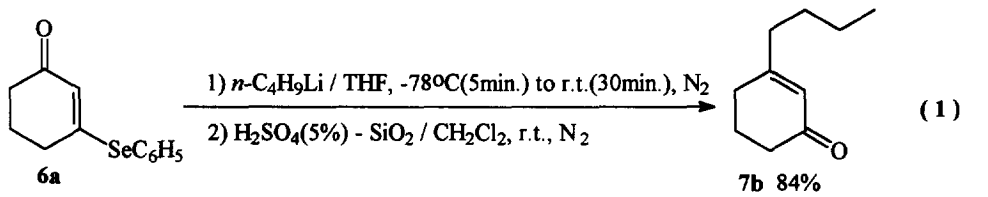
Initially we have addressed the problem of the acid concentration. Compound **2a** (R = H, R^1 = H, R^2 = *n*-Bu), prepared by the addition of *n*-butyllithium to (*Z*)-3-phenylselanyl-2-propenal (**1a**)[3], was treated with H_2SO_4 over SiO_2 in CH_2Cl_2 at decreasing acid concentrations (30%, 10%, 5%, 1%) in reaction time ranging from 20 minutes to 48 hours. It was found that the higher yield of the hydrolysis product **3a** (90%) can be achieved after 24 hours at room temperature even at reduced acid concentration (5% H_2SO_4). Therefore, these conditions were considered as optimal for the subsequent hydrolysis reactions. Several other hydrolysing systems such as CF_3CO_2H[4], $HgCl_2/CH_3CN$-H_2O[4], $TiCl_4$[5], AcOH, $HClO_4$[6], TsOH/dioxane-H_2O have also been tested. The former three systems gave unsatisfatory results, and among the others, the milder TsOH/dioxane-H_2O system promoted hydrolysis reactions in higher yields at room temperature. In some cases this system led to superior results comparing to the H_2SO_4/SiO_2 system.

In order to establish the scope of this 1,3-carbonyl transposition, the two-step-sequence described in Scheme 1 was also applied to β-phenylseleno-cyclohexenones **6**, which were prepared from β-halo-cyclohexenones **4**[7,8] and **5**[9,10] (Scheme 3).



Scheme 3

Addition of *n*-butyllithium to **6a** followed by hydrolysis of the crude product gave the expected enone **7b** in 84% overall yield after silica gel column chromatography (Equation 1).



(1)

Since many Grignard reagents are easier to prepare than organolithiums, we have performed the first step of the sequence using organomagnesium reagents instead of the lithium ones, in order to check any significant changes in the transposition yields. Compound **1a** (Entries 4 and 5; Table 1) was treated with *n*-BuMgBr and the crude product submitted to hydrolysis reaction. (*E*)-Hepten-1-al (**3a**) was obtained in 44% overall yield, much lower than the 80% observed when *n*-BuLi was used as the organometallic reagent. Similar results were also observed on the cyclic substrate **6a**, which led to lower 1,3-transposition yields (60%) when a Grignard reagent (methyl magnesium iodide) was employed instead of a organolithium (Entries 12 and 13; Table 1). In this case the hydrolysis step occurred during the aqueous work-up without any further acidic treatment, and phenyl methyl selenide was detected by GC-MS as the main byproduct in 40% yield, presumably resulting from the attack of the methyl magnesium bromide to the selenium atom of the enone. Additional experiments using different aliphatic Grignard reagents (Entries 14, 16 and 17; Table 1) for the addition step were performed, and complex mixtures of crude products were detected by TLC and GC. Further hydrolysis led to low yields of the expected transposition products. Reaction of **6a** with phenyl magnesium bromide (Entry 18; Table 1) gave after aqueous workup a mixture of products consisting mainly in diphenylselenide in 65% yield, resulting from the preferential attack to the selenium atom of the enone. In view of these results we concluded that organolithiums are superior to the Grignard reagents to perform the first step of the transposition sequence.

Table 1. 1,3-Carbonyl Transposition on β-Phenylseleno-α,β-Unsaturated Carbonyl Compounds.

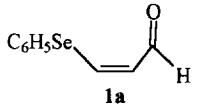
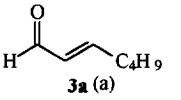
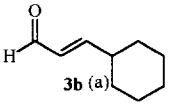
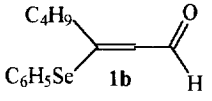
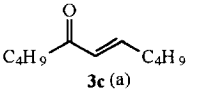
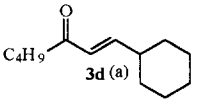
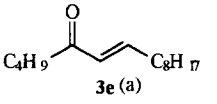
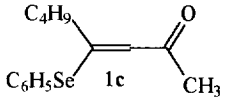
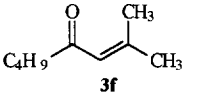
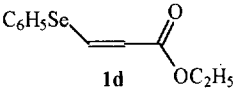
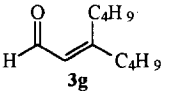
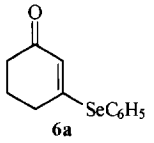
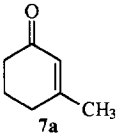
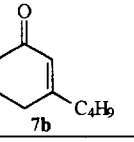
Entry	Vinylic Selenide	Organometallic Reagent	Hydrolysis Condition Time (h)	Product	Yield (%)
1	 **1a**	*n*-C_4H_9Li	A(24)	 **3a** (a)	62
2			A(0.3)		100
3			B(14)		82
4			C(24)		80
5		*n*-C_4H_9MgBr (1.2eq.)	C(24)		44
6		*c*-$C_6H_{11}MgBr$ (1.2eq.)	A(24)	 **3b** (a)	49[b]
7	 **1b**	*n*-C_4H_9Li	A(24)	 **3c** (a)	60
8		*c*-$C_6H_{11}MgBr$ (1.2eq.)	A(24)	 **3d** (a)	45
9		*n*-$C_8H_{17}MgBr$ (1.2eq.)	A(24)	 **3e** (a)	71
10	 **1c**	CH_3Li	D(24)	 **3f**	88
11	 **1d**	*n*-C_4H_9Li (2eq.)	A(24)	 **3g**	48[b]
12	 **6a**	CH_3MgI (1.2eq.)	none	 **7a**	60
13		CH_3Li (1.2eq.)	D(3.5)	**7a**	95
14		*n*-C_4H_9MgBr (1.2eq.)	C(24)	 **7b**	58

Table 1. (continued).

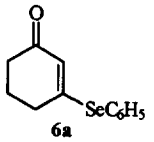
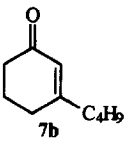
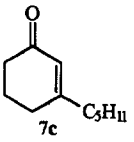
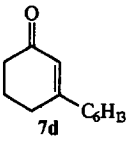
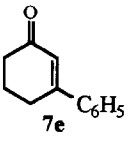
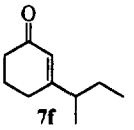
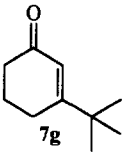
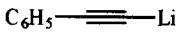
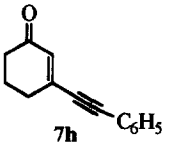
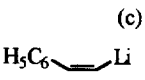
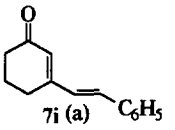
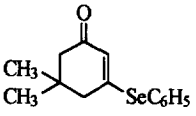
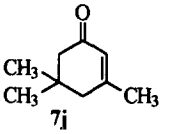
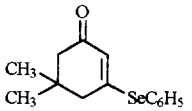
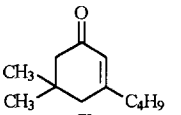
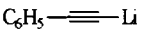
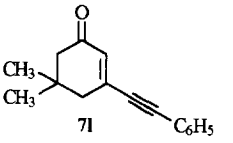
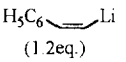
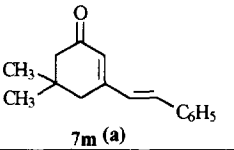
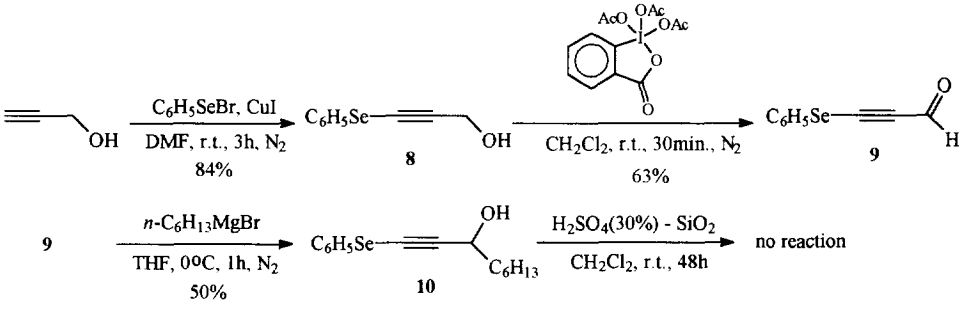
Entry	Vinylic Selenide	Organometallic Reagent	Hydrolysis Condition Time (h)	Product	Yield (%)
15	 **6a**	*n*-C_4H_9Li (1.1eq.)	D(2)	 **7b**	86
16		*n*-$C_5H_{11}MgBr$ (1.2eq.)	C(24)	 **7c**	46
17		*n*-$C_6H_{13}MgBr$ (1.2eq.)	C(24)	 **7d**	34
18		C_6H_5MgBr (1.2eq.)	none(none)	 **7e**	13
19		*s*-C_4H_9Li (1.1eq.)	D(2)	 **7f**	79
20		*t*-C_4H_9Li (1.2eq.)	D(3)	 **7g**	88
21	 (1.1eq.)		D(2.5)	 **7h**	84
22	 (1.1eq.)		D(2)	 **7i (a)**	96
23	 **6b**	CH_3Li (1.1eq.)	D(4)	 **7j**	92

Table 1. (continued).

Entry	Vinylic Selenide	Organometallic Reagent	Hydrolysis Condition Time (h)	Product	Yield (%)
24	 **6b**	*n*-C_4H_9Li (1.1eq.)	D(48)	 **7k**	65
25		 (1.1eq.)	D(12)	 **7l**	39
26		(c)  (1.2eq.)	D(12)	 **7m** (a)	41[(b)]

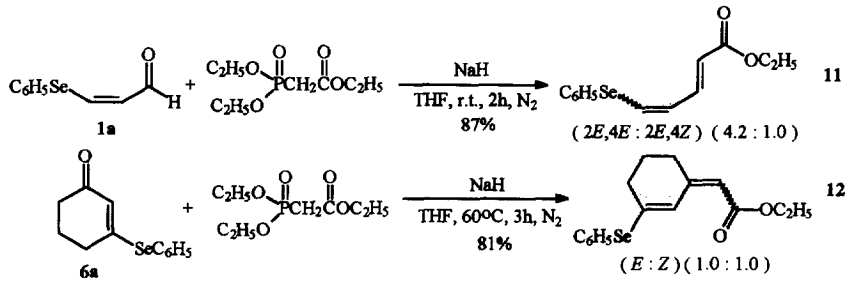
A : H_2SO_4 (30%) - SiO_2 ; B : H_2SO_4 (10%) - SiO_2 ; C : H_2SO_4 (5%) - SiO_2 ; D : TsOH
(a) the product presents pure *E* geometry at the C=C bond.
(b) calculated by GC-MS of the crude hydrolysis product.
(c) transmetalated from (*Z*)-butyl styryl telluride.

The generality of the organolithium route was demonstrated by reacting enones **6a** and **6b** with primary, secondary, tertiary, vinyl and ethynyllithiums (Table 1). The (*Z*)-styryllithium (Entries 22 and 26; Table 1) was obtained by a transmetalation reaction of (*Z*)-butyl styryl telluride with *n*-butyllithium[11]. The transposition products using this organolithium reagent showed isomerized styryl carbon-carbon double bond from *Z* to *E*; such isomerization occurred during the acid hydrolysis step, since the transmetalation reaction is known to preserve the double bond geometry[11]. An attempt to perform 1,3-carbonyl transposition by this method on 3-phenylselanyl-2-propynal (**9**)[12,13] proved unsuccessful, resulting in the recovery of the starting material (Scheme 4).



Scheme 4

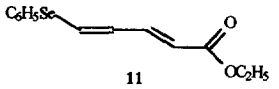
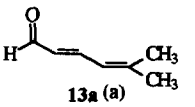
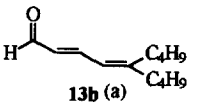
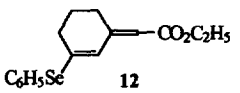
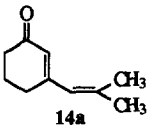
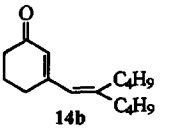
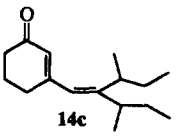
This carbonyl transposition sequence has also been tested on selenium dienoates. Two selenodienoic esters **11** and **12** in isomeric mixtures has been prepared by the Horner-Emmons reaction[14] (Scheme 5) and the isomeric ratios were determined by ^1H NMR.



Scheme 5

Since 1,5-carbonyl transposition has only been subject of a limited amount of investigation, consisting mainly in intramolecular hydride transfer[2], we have decided to submit selenides **11** and **12** to the addition/hydrolysis sequence in order to determine the scope of this methodology. Table 2 shows the results of these studies, performed on **11** and **12** with commercial organolithium reagents followed by hydrolysis reactions of the crude products, leading to the carbonyl transposed, selenium free dieno aldehydes and ketones in moderate to good yields. Attempts of using *t*-butyllithium, (*Z*)-styryl[11] and ethynyllithiums as organometallic additions reagents did not gave the expected 1,5-transposition products due to lack of addition reaction or decomposition during hydrolysis step.

Table 2. 1,5-Carbonyl Transposition on Selenium Dienoates.

Entry	Vinylic Selenide	Organometallic Reagent	Hydrolysis Condition Time (h)	Product	Yield (%)
1	 **11**	CH_3Li (2eq.)	A(24)	 **13a (a)**	59
2			B(12)		70
3		*n*-C_4H_9Li (2eq.)	B(12)	 **13b (a)**	95
4	 **12**	CH_3Li (2eq.)	B(4)	 **14a**	73
5		*n*-C_4H_9Li (2.2eq.)	B(4)	 **14b**	88
6		*s*-C_4H_9Li (2eq.)	B(2.5)	 **14c**	49

A : H_2SO_4 (5%) - SiO_2 ; B : TsOH

(a) the product presents pure *E* geometry at the C=C bond.

CONCLUSION

The addition/hydrolysis sequence is a useful method to perform 1,3 and 1,5-carbonyl transposition on β-seleno and γ-seleno carbonyl conjugated vinylic selenides. The addition reaction using organolithium reagents a furnishes better results than with the Grignard ones, and the milder H_2SO_4 (5%)-SiO_2 or TsOH systems in the hydrolysis step often lead to the highest transposition overall yields.

EXPERIMENTAL SECTION

General

^{1}H NMR spectra were determined in $CDCl_3$ on a Bruker AC-200 spectrometer with tetramethylsilane as internal standard. ^{13}C NMR spectra were obtained on a Bruker AC-200 spectrometer using the central peak of $CDCl_3$ (77.0 ppm) as standard. IR spectra were obtained on a Perkin Elmer 1600 spectrophotometer. Low resolution mass spectra were obtained on a Finnigan 4021 spectrometer or on a GC/MS - Hewlett Packard 5988-8/5890 spectrometer, both operating at 70 eV. Elemental analyses were performed by the Microanalytical Laboratory of the Institute of Chemistry - USP. Flash column chromatography were carried out on Merck silica gel (grade 60, 230-400 mesh). All solvents used in reactions were dried according to standard procedure. THF and ether were distilled from sodium/benzophenone under N_2 atmosphere immediately before use. Selenium (320 mesh) was purchased from Aldrich. *n*-BuLi, *s*-BuLi and *t*-BuLi solutions were purchased from Aldrich and titrated prior to use. All operations except for the hydrolysis reactions were carried out in flame dried glassware, under dried and deoxygenated N_2 atmosphere. The selenide **1a**[3] and the compounds **4a**[7], **4b**[7] and **5**[9] were prepared by described methods. Compounds **3c-g**, **7b-i**, **7k**, **7m**, **13a**, **13b** and **14a** were previously known.[19]

Preparation of 1-phenylselanyl-1-hepten-3-ol (2a). *n*-Butyllithium (2.6 ml, 5.0 mmol, 2.0 M solution in hexane) was added dropwise to a stirred solution of (*Z*)-3-phenylselanyl-2-propenal (**1a**) (1.056 g, 5.0 mmol) in THF (5 ml) under N_2 atmosphere, at -78°C, stirring for 5 minutes and then 30 mintures at room temperature. The reaction was quenched with saturated NH_4Cl solution and extracted with ether. The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$ and the solvents were evaporated. The residue was purified by silica gel column chromatography (9 : 1 hexane / ethyl acetate) to yield 1.560 g of **2a** (89 %). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 - 0.98 (m, 6 H), 1.13 - 1.36 (m, 8 H), 1.40 - 1.68 (m, 4 H), 2.04 (brs, 1 H), 2.22 (brs, 1 H), 4.13 (dt, J_1 = J_2 = 6 Hz, 1 H), 4.44 (dt, J_1 = J_2 = 6 Hz, 1 H), 5.97 (dd, J = 15 Hz, J = 6 Hz, 1 H), 6.03 (dd, J = 9 Hz, J = 6 Hz, 1 H), 6.55 (d, J = 9 Hz, 1 H), 6.64 (d, J = 15 Hz, 1 H), 7.26 - 7.35 (m, 6 H), 7.44 - 7.50 (m, 4 H) (mixture of isomers *Z* : *E*, 1.0 : 1.6). ^{13}C NMR (50

MHz, $CDCl_3$) δ 13.9, 22.4, 22.5, 27.2, 27.3, 36.3, 36.6, 71.0, 73.3, 119.3, 122.4, 127.1, 127.2, 129.1, 131.9, 132.3, 136.1, 138.9. IR (neat) ν_{cm-1} 1073, 1439, 1478, 1579, 3360. LRMS (rel. int.) m/z (isomers a, b) 270 (M^+, 44, 39), 213 (43, 38), 195 (15, 12), 185 (50, 45), 157 (41, 37), 133 (73, 65), 113 (46, 38), 104 (82, 76), 85 (92, 86), 77 (66, 59), 57 (100, 100). Anal. Calcd. for $C_{13}H_{18}OSe$: C, 57.99, H, 6.74. Found : C, 57.95, H, 6.74.

Preparation of phenylselenol[15]. Typical procedure. A solution of diphenyl diselenide (5.959 g, 19.0 mmol) and hypophosphorus acid (13 ml, 50 % wt solution in water) in THF (33 ml) under N_2 atmosphere was refluxed for 20 minutes. The mixture was then extracted with benzene, washed with brine, dried over anhydrous $MgSO_4$ and the solvents were evaporated. The crude phenylselenol was immediately used without purification.

Preparation of 3-phenylselanyl-2-heptenal (1b)[16]. To a solution of 2-heptynal[17] (2.203 g, 20.00 mmol) and potassium bicarbonate (0.116 g, 0.84 mmol) in *t*-butanol (3.2 ml) and THF (16.6 ml) at room temperature, under N_2 atmosphere, was added dropwise phenylselenol recently prepared (from diphenyl diselenide 2.604 g, 8.34 mmol). The mixture was stirred for 30 minutes, quenched with saturated $NaHCO_3$ solution and extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and the solvents were evaporated. The residue was purified by silica gel column chromatography (98 : 2 hexane / ethyl acetate) to yield 2.759 g of **1b** (62 %). ^1H NMR (200 MHz, $CDCl_3$) δ 0.72 (t, J = 7 Hz, 3 H), 1.02 - 1.20 (m, 2 H), 1.31 - 1.46 (m, 2 H), 2.27 (t, J = 7 Hz, 2 H), 6.53 (d, J = 4 Hz, 1 H), 7.31 - 7.41 (m, 3 H), 7.62 (dd, J = 7 Hz, J = 2 Hz, 2 H), 9.87 (d, J = 4 Hz, 1 H) (single isomer). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 21.8, 31.6, 38.1, 124.9, 129.1, 129.2, 136.3, 189.8. IR (neat) ν_{cm-1} 1535, 1672, 2743, 2824. LRMS (rel. int.) m/z 268 (M^+, 37), 191 (6), 158 (48), 145 (12), (7), 111 (31), 93 (68), 77 (100), 67 (66), 51 (72). Anal. Calcd. for $C_{13}H_{16}OSe$: C, 58.43, H, 6.03. Found : C, 58.51, H, 6.08.

Preparation of 4-phenylselanyl-3-octen-2-one (1c)[16]. Phenylselenol (recently prepared from diphenyl diselenide 1.302 g, 4.17 mmol) was added dropwise to a solution of 3-octyn-2-one[17] (1.242 g, 10 mmol) in ether (8.3 ml) at 0°C, under N_2 atmosphere. Piperidine (3 drops, catalytic amount) was added and the mixture was stirred for 30 minutes at 0°C and then the solvents were evaporated. The residue was purified by silica gel column chromatography (95 : 5 hexane / ethyl acetate) to yield 1.501 g of **1c** (64 %). ^1H NMR (200 MHz, $CDCl_3$) δ 0.66 (t, J = 7 Hz, 3 H), 0.94 - 1.12 (m, 2 H), 1.23 - 1.38 (m, 2 H), 2.16 - 2.25 (m, 5 H), 6.67 (s, 1 H), 7.26 - 7.40 (m, 3 H), 7.63 - 7.67 (m, 2 H) (single isomer). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.4, 21.9, 30.1, 32.2, 37.4, 121.4, 128.3, 128.9, 137.3, 165.5, 196.5. IR (neat) ν_{cm-1} 1359, 1539,

1661. LRMS (rel. int.) m/z 283 (100), 282 (M^+, 51), 205 (9), 125 (40), 107 (9), 95 (9), 77 (6), 51 (9). Anal. Calcd. for $C_{14}H_{18}OSe$: C, 59.79, H, 6.45. Found : C, 59.61, H, 6.39.

Preparation of ethyl-3-phenylselanyl-2-propenate (1d)[16]. Phenylselenol (recently prepared from diphenyl diselenide 5.959 g, 19.0 mmol) was added dropwise to a solution of ethyl propiolate (2.929 g, 29.9 mmol) in ether (10 ml) at 0°C, under N_2 atmosphere, followed by the addition of piperidine (3 - 4 drops, catalytic amount). The reaction mixture was stirred for 15 minutes at 0°C and then 4 hours at room temperature. After dilution with ether, the mixture was washed with saturated NH_4Cl solution and brine, respectively. The combined organic layers were dried over anhydrous $MgSO_4$ and the solvents were evaporated. The residue was purified by distillation to yield 4.685 g of **1d** (61 %). bp = 100°C / 0.2 mmHg. ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7 Hz, 3 H), 1.32 (t, *J* = 7 Hz, 3 H), 4.15 (q, *J* = 7 Hz, 2 H), 4.26 (q , *J* = 7 Hz, 2 H), 5.86 (d, *J* = 15 Hz, 1 H), 6.35 (d, *J* = 9 Hz, 1 H), 7.24 - 7.39 (m, 6 H), 7.55 - 7.62 (m, 4 H), 7.74 (d, *J* = 9 Hz, 1 H), 8.14 (d, J = 15 Hz, 1 H) (mixture of isomers *Z* : *E*, 4.6 : 1.0). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 14.3, 60.2, 60.4, 116.7, 120.6, 126.3, 128.1, 128.9, 129.3, 129.7, 132.5, 133.1, 134.8, 144.2, 149.7, 164.5, 167.1. IR (neat) ν_{cm-1} 1152, 1206, 1570, 1693. LRMS (rel. int.) m/z (isomers a, b) 256 (M^+, 70, 89), 211 (24, 32), 183 (96, 96), 157 (42, 43), 147 (12, 14), 131 (49, 44), 117 (9, 9), 103 (38, 41), 91 (19, 13), 77 (100, 100), 65 (13, 12). Anal. Calcd. for $C_{11}H_{12}O_2Se$: C, 51.78, H, 4.74. Found : C, 51.79, H, 4.81.

Preparation of 1-phenylselanyl-1-cyclohexen-3-one (6a). To a solution of diphenyl diselenide (0.173 g, 0.43 mmol) in ethanol (1.6 ml) at room temperature, under N_2 atmosphere, was added sodium borohydride (0.033 g, 0.87 mmol) in small portions. The mixture was cooled to 0°C then acetic acid (0.16 ml) and a solution of iodide **4a**[7] (0.200 g, 0.90 mmol) in ethanol (0.5 ml) were added, respectively. The reaction mixture was stirred at room temperature for 6 hours, quenched with a 10 % $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and the solvents were evaporated. The residue was purified by silica gel column chromatography (8 : 2 hexane / ethyl acetate) to yield 0.160 g of **6a** (75 %). ^1H NMR (200 MHz, $CDCl_3$) δ 1.90 - 2.08 (tt, $J_1 = J_2 = 6$ Hz, 2 H), 2.37 (t, *J* = 6 Hz, 2 H), 2.56 (t, *J* = 6 Hz, 2 H), 5.76 (s, 1 H), 7.32 - 7.46 (m, 3 H), 7.55 - 7.59 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.1, 31.2, 37.1, 125.0, 125.3, 129.6, 129.8, 136.6, 165.6, 195.5. IR (neat) ν_{cm-1} 1573, 1662. LRMS (rel. int.) m/z 252 (M^+, 11), 224 (3), 196 (3), 171 (11), 157 (5), 143 (3), 128 (1), 115 (5), 102 (1), 95 (7), 77 (13), 67 (100), 51 (12). Anal. Calcd. for $C_{12}H_{12}OSe$: C, 57.38, H, 4.82. Found : C, 57.33, H, 4.78.

Preparation of 5,5-dimethyl-1-phenylselanyl-1-cyclohexen-3-one (6b). Method A. Sodium borohydride (0.737 g, 19.4 mmol) was added in small portions to a solution of diphenyl diselenide (2.996 g, 9.6 mmol) in ethanol (36 ml) at room temperature, under N_2 atmosphere. The mixture was then cooled to 0°C then acetic acid (3.56 ml) and a solution of iodide **4b**[7] (5.002 g, 20.0 mmol) in ethanol (11 ml) were added, respectively. The reaction mixture was stirred at room temperature for 6 hours, quenched with a 10 % $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and the solvents were evaporated. The residue was purified by silica gel column chromatography (9 : 1 hexane / ethyl acetate) to yield 4.950 g of **6b** (92 %). **Method B.** A solution of diphenyl diselenide (1.545 g, 4.95 mmol) and tributylphosphine (1.093 g, 5.40 mmol) in THF (9 ml) was stirred for 5 minutes at room temperature, under N_2 atmosphere. To this was added 10 % NaOH solution (3.56 ml) and the mixture was stirred for further 15 minutes at room temperature. Then the phenylselenolate solution thus prepared was added dropwise to a solution of chloride **5**[9] (1.428 g, 9.00 mmol) in THF (4.5 ml) at room temperature, under N_2 atmosphere, stirring for 15 minutes. The reaction mixture was diluted with ether, washed with brine, dried over anhydrous $MgSO_4$ and the solvents were evaporated. The residue was purified by silica gel column chromatography (9 : 1 hexane / ethyl acetate) to yield 2.408 g of **6b** (95 %). ^1H NMR (200 MHz, $CDCl_3$) δ 1.03 (s, 6 H), 2.20 (s, 2 H), 2.42 (s , 2 H), 5.76 (s , 1 H), 7.34 - 7.37 (m, 3 H), 7.53 - 7.57 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.9, 34.5, 44.9, 50.9, 124.3, 125.2, 129.6, 129.8, 136.6, 163.7, 195.7. IR (neat) ν_{cm-1} 1577, 1661. LRMS (rel. int.) m/z 280 (M^+, 11), 199 (23), 171 (1), 157 (7), 115 (7), 95 (5), 77 (25), 67 (100). Anal. Calcd. for $C_{14}H_{16}OSe$: C, 60.22, H, 5.78. Found : C, 60.40, H, 5.79.

Preparation of ethyl 5-phenylselanyl-2,4-pentadienoate (11). To a suspension of sodium hydride (0.619 g, 12.89 mmol, 50 % dispersion in mineral oil, previously washed with dry hexane) in THF (26 ml) at room temperature, under N_2 atmosphere, was added dropwise triethyl phosphonoacetate (2.890 g, 12.89 mmol). After 15 minutes of stirring, the selenide **1a** was added slowly. The reaction mixture was stirred for 2 hours at room temperature, then quenched with water and extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and the solvents were evaporated. The residue was purified with silica gel column chromatography (9 : 1 hexane / ethyl acetate) to yield 1.850 g of **11** (87 %). ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 7 Hz, 3 H), 1.30 (t, J = 7 Hz, 3 H), 4.17 (q , J = 7 Hz, 2 H), 4.22 (q, J = 7 Hz, 2 H), 5.69 (d, J = 15 Hz, 1 H), 5.95 (d, J = 15 Hz, 1 H), 6.39 (dd, J = 15 Hz, J = 11 Hz, 1 H), 6.62 (dd, J = 11 Hz, J = 9 Hz, 1 H), 7.01 (d , J = 9 Hz, 1 H), 7.20 (d , J = 15 Hz, J = 11 Hz, 1 H), 7.23 (dd, J = 15 Hz, J = 11 Hz, 1 H), 7.29 - 7.37 (m, 6 H), 7.46 - 7.59 (m, 4 H) (mixture of isomers 2*E*,4*E* : 2*E*,4*Z*, 4.2 : 1.0). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 60.1, 60.3, 118.7, 122.5, 127.7, 127.9, 128.3, 129.3, 129.5, 129.6, 129.8, 132.5, 132.8, 133.7, 134.4, 135.3, 139.9, 142.9, 166.9, 167.0. IR (neat)

ν_{cm-1} 1126, 1160, 1216, 1264, 1567, 1620, 1708. LRMS (rel. int.) m/z (isomers a, b) 282 (M^+, 1, 4), 237 (2, 2), 209 (1, 1), 157 (11, 10), 125 (58, 45), 97 (100, 100), 77 (14, 13). Anal. Calcd. for $C_{13}H_{14}O_2Se$: C, 55.52, H, 5.02. Found : C, 55.54, H, 5.11.

Preparation of ethyl 2-(3-phenylselanyl-2-cyclohexenyliden) acetate (12). To a suspension of sodium hydride (0.413 g, 8.6 mmol, 50 % dispersion in mineral oil, previously washed with dry hexane) in THF (17 ml at room temperature, under N_2 atmosphere, was added dropwise triethyl phosphonoacetate (1.928 g, 8.6 mmol). After 15 minutes of stirring, the selenide **6a** (1.080 g, 4.3 mmol) was added slowly. The reaction mixture was warmed to 60°C, stirred for 3 hours, then quenched with water and extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvents were evaporated. The residue was purified by silica gel column chromatography (9 : 1 hexane / ethyl acetate) to yield 1.119 g of **12** (81 %). ^1H NMR (200 MHz, $CDCl_3$) δ 1.18 (t, *J* = 7 Hz, 3 H), 1.24 (t, *J* = 7 Hz, 3 H), 1.72 - 1.80 (m, 4 H), 2.34 (t, *J* = 6 Hz, 4 H), 2.93 (t, *J* = 6 Hz, 4 H), 4.07 (q, *J* = 6 Hz, 2 H), 4.11 (q, *J* = 6 Hz, 2 H), 5.36 (s, 1 H), 5.37 (s, 1 H), 6.04 (s, 1 H), 7.32 - 7.35 (m, 7 H), 7.53 - 7.58 (m, 4 H) (mixture of isomers *E* : *Z*, 1 : 1). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.2, 22.8, 23.3, 25.5, 31.3, 31.7, 31.8, 59.3, 59.5, 111.5, 113.4, 124.4, 128.4, 128.5, 129.2, 129.3, 135.5, 135.7, 145.7, 146.9, 150.4, 152.8, 166.1, 167.0. IR (neat) ν_{cm-1} 1152, 1191, 1234, 1258, 1578, 1605, 1704. LRMS (rel. int.) m/z 322 (M^+, 28 , 28), 277 (9, 9), 250 (12, 13), 241 (8, 8), 213 (29, 29), 197 (32, 31), 169 (30, 29), 157 (17, 15), 137 (28, 28), 119 (20, 20), 91 (100, 100), 77 (34, 33), 65 (24, 24). Anal. Calcd. for $C_{16}H_{18}O_2Se$: C, 59.82, H, 5.65. Found : C, 59.92, H, 5.78.

Preparation of 3-phenylselanyl-2-propynal (9). To a suspension of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3 (1*H*)-one[13] (2.381 g, 5.6 mmol) in dry CH_2Cl_2 (23 ml) at room temperature, under N_2 atmosphere, was added a solution of selenide **8**[12] (1.000 g, 4.7 mmol) in dry CH_2Cl_2 (19 ml). After stirring for 30 minutes, the mixture was diluted with ether and a 1.3 M NaOH solution was added dropwise until the reaction mixture became homogeneous. The organic layer was separated, washed with water, dried over anhydrous $MgSO_4$ and the solvents were evaporated. The residue was purified by silica gel column chromatography (8 : 2 hexane / ethyl acetate) to yield 0.620 g of **9** (63 %), which was not much stable and was submitted to the next reaction immediately after its purification. ^1H NMR (200 MHz, $CDCl_3$) δ 7.34 - 7.37 (m, 3 H), 7.53 - 7.58 (m , 2 H), 9.16 (s , 1 H). LRMS (rel. int.) m/z 210 (M^+, 15), 182 (21), 154 (2), 129 (6), 102 (100), 89 (13), 77 (32), 63 (4), 51 (57).

Preparation of 1-phenylselanyl-1-nonyn-3-ol (10). To a solution of the Grignard reagent, prepared from hexyl bromide (0.719 g, 4.3 mmol) and magnesium (0.110 g, 4.5 mmol) in THF (8 ml), at 0°C under N_2

atmosphere, was added dropwise a solution of **9** (0.62 g, 3.0 mmol) in THF (3.8 ml). The reaction mixture was stirred for 1 hour at room temperature, then quenched with a saturated NH_4Cl solution and extracted with ether. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and the solvents were evaporated. The residue was purified by silica gel column chromatography (9 : 1 hexane / ethyl acetate) to yield 0.440 g of **10** (50 %). ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 6 Hz, 3 H), 1.25 - 1.52 (m, 8 H), 1.71 - 1.82 (m, 2 H), 2.05 (brs, 1 H), 4.57 (t, J = 6 Hz, 1 H), 7.21 - 7.35 (m, 3 H), 7.48 - 7.54 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 22.5, 25.1, 28.9, 31.7, 37.7, 63.5, 64.9, 104.8, 127.1, 128.4, 128.8, 129.0, 129.5. IR (neat) ν_{cm-1} 2171, 3339. LRMS (rel. int.) m/z 265 (2), 253 (4), 214 (7), 183 (34), 157 (14), 141 (9), 128 (11), 115 (25) 102 (100), 91 (47), 77 (81), 67 (23), 51 (84). Anal. Calcd. for $C_{15}H_{20}OSe$: C, 61.01, H, 6.83. Found : C, 61.02, H, 6.75.

Addition reaction with commercial organolithium. Typical procedure. *n*-Butyllithium (1.0 ml, 2.0 mmol, 2.0 M solution in hexane) was added dropwise to a stirred solution of **6a** (0.502 g, 2.0 mmol) in THF (2 ml) at -78°C, under N_2 atmosphere. The reaction mixture was stirred for 5 minutes at -78°C and then 30 minutes at room temperature. The reaction was quenched with saturated NH_4Cl solution and extracted with ether. The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$ and the solvents were evaporated. The crude product was submitted directly to the hydrolysis reaction.

Addition reaction with Grignard reagent. Typical procedure. *n*-Butylmagnesium bromide (1.8 ml, 3.6 mmol, 2 M solution in THF, previously prepared) was added dropwise to a stirred solution of **6a** (0.754 g, 3.0 mmol) in THF (6 ml) at 0°C, under N_2 atmosphere. The reaction mixture was stirred for 5 minutes at 0°C, and then 1 hour at room temperature. The reaction was worked up as above mentioned and the crude product was submitted directly to the hydrolysis reaction.

Addition reaction with lithium phenylacetylide. Typical procedure. *n*-Butyllithium (1.0 ml, 2.0 mmol, 2.0 M solution in hexane) was added dropwise to a stirred solution of phenylacetylene (0.204 g, 2.0 mmol) in THF (4 ml) at -78°C, under N_2 atmosphere. The reaction mixture was stirred for 40 minutes at -78°C and to this was added dropwise a solution of **6a** (0.502 g, 2.0 mmol) in THF (2 ml), stirring for further 40 minutes at -78°C and then 30 minutes at room temperature. The reaction was worked up as above mentioned and the crude product was submitted directly to the hydrolysis reaction.

Addition reaction with (*Z*)- styryl lithium. Typical procedure. *n*-Butyllithium (1.0 ml, 2.0 mmol, 2.0 M solution in hexane) was added dropwise to a stirred solution of (*Z*)-butyl styryl telluride[18] (0.576 g, 2.0 mmol) in THF (4 ml) at -78° C , under N_2 atmosphere. The reaction mixture was stirred for 40 minutes at

-78°C and to this was added dropwise a solution of **6a** (0.502 g, 2.0 mmol) in THF (2 ml), stirring for further 40 minutes at -78°C and then 30 minutes at room temperature. The reaction was worked up as above mentioned and the crude product was submitted directly to the hydrolysis reaction.

Hydrolysis reaction with aqueous H_2SO_4 solution. Typical procedure. The crude product of the addition reaction of **6a** (2.0 mmol) with *n*-butyllithium (2.0 mmol) was dissolved in CH_2Cl_2 (7.5 ml), and added to a suspension of silica gel (3.60 g, 70 - 230 mesh) and aqueous H_2SO_4 solution (0.55 ml, e.g. 5 % v / v) in CH_2Cl_2 (7.5 ml) at room temperature. The reaction mixture was stirred for 24 hours, then filtered through a glass funnel and the filtrate thoroughly washed with CH_2Cl_2. The combined organic layers were neutralized with saturated $NaHCO_3$ solution, washed with brine, dried over anhydrous $MgSO_4$ and the solvents were evaporated. The residue was purified by silica gel column chromatography (9 : 1 hexane / ethyl acetate) to yield 0.256 g of 1-butyl-1-cyclohexen-3-one (**7b**) (84 %).

Hydrolysis with *p*-toluenesulfonic acid. Typical procedure. The crude product of the addition reaction of **6a** (2.0 mmol) with *n*-butyllithium (2.2 mmol) was treated with a solution of *p*-toluenesulfonic acid (20 ml, 1 M solution in dioxane / water, 3 : 1 v / v), stirring for 2 hours at room temperature. The reaction mixture was then diluted with ether, neutralized with 10 % $NaHCO_3$ solution and washed with brine. The combined organic layers were dried over $MgSO_4$ and the solvents were evaporated. The residue was purified as above mentioned to yield 0.262 g of **7b** (86 %).

5,5-Dimethyl-1-(2-phenyl-1-ethynyl)-1-cyclohexen-3-one (7 l). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 (s, 6 H), 2.29 (s, 3 H), 2.43 (d, J =1 Hz, 3 H), 6.30 (t, J =1 Hz, 1 H), 7.30 - 7.38 (m, 3 H), 7.44 - 7.51 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.1, 28.2, 33.7, 44.3, 51.0, 88.7, 99.3, 122.0, 124.5, 128.5, 129.4, 131.3, 131.9, 141.2, 199.0. IR (neat) ν_{cm-1} 1666 , 2198 . LRMS (rel. int.) m/z 224 (M^+, 80), 209 (16), 181 (25), 168 (93), 139 (100), 115 (16), 77 (10), 63 (13), 51 (14). Anal. Calcd. for $C_{16}H_{16}O$: C, 85.68, H, 7.19. Found : C, 85.37, H, 7.12.

1-(2-Butyl-1-hexenyl)-1-cyclohexen-3-one (14 b). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (t , J = 8 Hz , 3 H), 0.91 (t, J = 8 Hz, 3 H), 1.15 - 1.45 (m, 8 H), 1.97 (t, J = 6 Hz, 2 H), 2.07 (t, J = 8 Hz, 2 H), 2.22 (t, J = 8 Hz, 2 H), 2.38 (t, J = 6 Hz, 4 H), 5.73 (s, 1 H), 5.89 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 14.0, 22.3, 22.7, 30.2, 30.4, 30.6, 31.5, 37.2, 37.6, 125.0, 126.2, 150.2, 159.4, 199.9. IR (neat) ν_{cm-1} 1575, 1605, 1627, 1670. LRMS (rel. int.) m/z 234 (M^+, 19), 191 (42), 177 (65), 150 (42), 135 (56), 121 (67), 107 (54), 91 (100), 79 (82), 67 (27), 55 (4). Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99, H, 11.18. Found : C, 82.06, H, 11.01.

1-(2-(*sec*-Butyl)-3-methyl-1-pentenyl)-1-cyclohexen-3-one (14 c). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.78 - 0.92 (m, 6 H), 0.98 - 1.06 (m, 6 H), 1.28 - 1.48 (m, 4 H), 1.97 - 2.12 (m, 3 H), 2.30 - 2.42 (m, 4 H), 2.73 - 2.84 (m, 1 H), 5.76 (d, J = 4 Hz, 1 H), 5.86 (d, J = 1 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.0, 12.4, 12.5, 13.9, 18.8, 22.2, 22.7, 22.8, 23.0, 27.5, 27.6, 28.9, 30.6, 30.8, 30.9, 31.4, 31.6, 35.0, 35.3, 37.3, 37.9, 38.0, 42.6, 123.4, 123.7, 126.2, 126.4, 158.2, 158.8, 160.5, 199.9. IR (neat) ν_{cm-1} 1459, 1606, 1670. LRMS (rel. int.) m/z 235 (100), 205 (18), 187 (6), 177 (36), 159 (16), 149 (23), 133 (10), 121 (23), 105 (21), 91 (31), 79 (17), 55 (38). Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99, H, 11.18. Found : C, 81.94, H, 11.05.

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ACKNOWLEDGMENTS

The authors acknowledge the following agencies for support : CNPq and FAPESP.

(*Received in USA* 5 *March* 1997; *accepted* 18 *April* 1997)