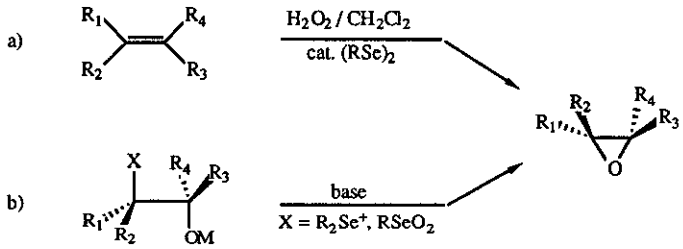
ORIGINAL SYNTHESES OF EPOXIDES INVOLVING ORGANOSELENIUM INTERMEDIATES.§

A. Krief *, W. Dumont, D. Van Ende, S. Halazy, D. Labar, J.-L. Laboureur, and Lê T. Q.
Facultés Universitaires Notre-Dame de la Paix. 61 rue de Bruxelles, 5000 Namur, Belgium.

Abstract - β-oxidoalkylselenonium salts and β-oxidoalkylselenones are valuable precursors of a large variety of epoxides. These species were synthesized by reaction of α-selenonio or α-selenonylalkylpotassium with carbonyl compounds or by reaction of a suitable base on β-hydroxyalkylselenonium salts or β-hydroxyalkylselenones, themselves obtained from β-hydroxyselenides. The most powerful method, based on the cyclization of β-hydroxyalkylselenonium salts is fully documented.

Organoselenium chemistry has provided over the last fifteen years valuable reagents able to perform chemo-, regio- and stereoselective transformations under mild conditions [1]. This proved inter alia the case of epoxides bearing hydrogens or hydrocarbon side chains on the ring whose synthesis has been efficiently achieved [1] by oxidation of olefins with hydrogen peroxide [2] in the presence of catalytic amounts of seleninic acids or by cyclization of β-oxidoalkylselenonium salts [1a,f,j,l,3-6] or β-oxidoalkylselenones [7] (Scheme 1).

Scheme 1.

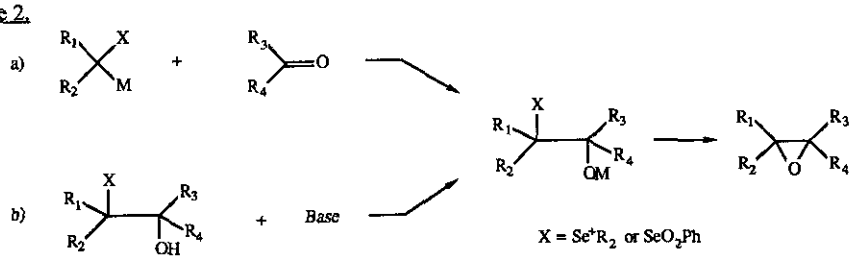


The aim of this review is to gather and to discuss the results involving the two latter intermediates which have been disclosed over the past fifteen years mainly from our laboratory.

The β-oxidoalkylselenonium salts and β-oxidoalkylselenones involved in this process (Scheme 1b) have been prepared in straightforward manner (i) from a carbonyl compound and α-selenonio or α-selenonyl alkyl potassium (Scheme 2a) or (ii) on reaction of a suitable base on β-hydroxyalkylselenonium salts or β-hydroxyalkylselenones (Scheme 2b) which were synthesized from β-hydroxyalkylselenides.

§ Dedicated to Professor D. H. R. Barton on the occasion of his seventieth birthday.

Scheme 2.



A. Synthesis of epoxides from selenonio or selenonyl alkyl potassium.

When we started this work we expected selenonium ylides to be more nucleophilic than their sulfur analogues [8] due to the longer carbon heteroatom bond which would have increased the reactivity of the carbanion by decreasing both its stabilization and its steric bulk. We hoped that these reagents would for example allow the synthesis of epoxides from deoxybenzoin or 2,2,6,6,-tetramethylcyclohexanone which are not available [9,10] from methylenedimethylsulfurane due to the complete enolisation of the former derivative and to the high steric hindrance around the carbonyl group of the second which preclude the desired reaction.

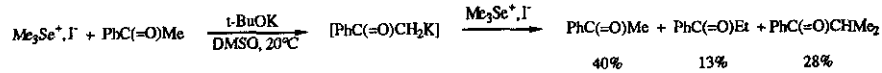
Thus arylsubstituted epoxides have been obtained [3] in almost quantitative yield by simple addition of potassium tert-butoxide on a mixture of aromatic aldehydes and trimethylselenonium iodide, diphenylmethyl- or diphenylethylselenonium tetrafluoroborates as well (Scheme 3).

Scheme 3.

	R	X	R_1	R_3	R_4	Yield %
a	Me, or Ph	BF_4	H	H	Ph	90
b	Me	I	H	H	p-MeO-Ph	75
c	Me	I	H	H	p-NC-Ph	54
d	Me	I	H	H	mesityl	79
e	Ph	BF_4	Me	H	Ph	69
f	Ph	BF_4	H	Ph	Ph	90
g	Me	I	H	H	PhCH=CH	71
h	Me	I	H	Ph	PhCH=CH	50

The required selenonium salts have been conveniently prepared [3a] from dimethylselenide and methyl iodide (neat, 90% yield) or from diphenylselenide and the corresponding alkyl iodide and silver tetrafluoroborate (CH_2Cl_2, 20°C ; Me, Et, iPr : 60, 50, 36% yield). The reaction occurs chemoselectively with cinnamaldehyde and chalcone and exclusively leads [3a] to the α,β-unsaturated epoxide (Scheme 3 entries g,h). It is unfortunately strictly limited at present [2] to non enolisable carbonyl compounds since under similar or closely related conditions enolisable-carbonyl compounds do not form significant amounts of the corresponding oxiranes[3a]. In the case of acetophenone and trimethylselenonium iodide, for example, polymethylation of the carbonyl compound occurs [3a] (Scheme 4). This result can be rationalized accounting that an enolate, which is then alkylated by the selenonium salt, is intermediarily produced.

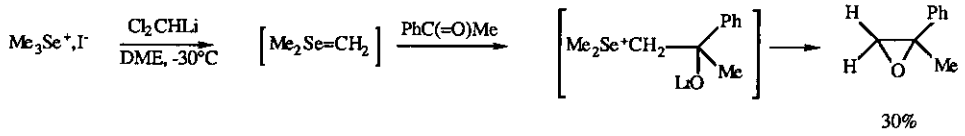
Scheme 4.



In order to overcome this problem, we decided to perform [3a] the reaction in two distinct steps and to react acetophenone on a preformed solution of methylenediphenylselenurane. We found that n-butyllithium is not a suitable base for the metalation of methylselenoniumdiphenylsulfonium fluoroborate since an exchange of ligands producing phenyllithium and leading finally to 1,1- diphenylethanol instead takes place [11], already at -78°C.

This type of reaction occurs with related sulfonium salts but to a minor extent [8] and at much higher temperature (0°C, 0.5h) than with alkyl aryl selenonium salts [11a]. Finally, the metalation was successfully achieved with dichloromethyllithium (LDA, CH_2Cl_2, DME, -78°C) and oxiranes have been obtained although in modest yield even on further addition of non-enolisable or enolisable carbonyl compounds (Scheme 5).

Scheme 5.

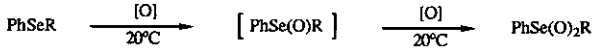


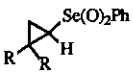
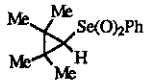
30%

Thus, although selenium ylides behave as their sulfur analogues, they are not, at present, as versatile and as easily available.

α-Metalloalkylphenylselenones readily available from the corresponding selenones and potassium alkoxides or potassium amides are also able to transform aldehydes and ketones to epoxides [7]. The reaction is best achieved by adding 1.5 equiv. of tert-BuOK on a 1.5/1 mixture of the selenone and the carbonyl compound and proceeds even with enolisable derivatives. It can be achieved with primary alkylphenylselenones [7] and cyclopropylphenylselenone [11,7b] which are both readily available by oxidation of the corresponding selenide with peracids [7b,12a], potassium permanganate [7b,12a] or hydrogen peroxide in the presence of seleninic acids [12b] (Scheme 6). The latter reaction is not general. It cannot yet be performed [12] on sec-alkylphenylselenides or on tetraalkyl substituted [7b] cyclopropane derivatives since in the former case, selenoxide elimination leading to a mixture of olefins instead takes place whereas, in the second one, the selenoxide intermediary produced can not be further oxidized [11] and has been isolated in good yield even when an excess of reagent is used.

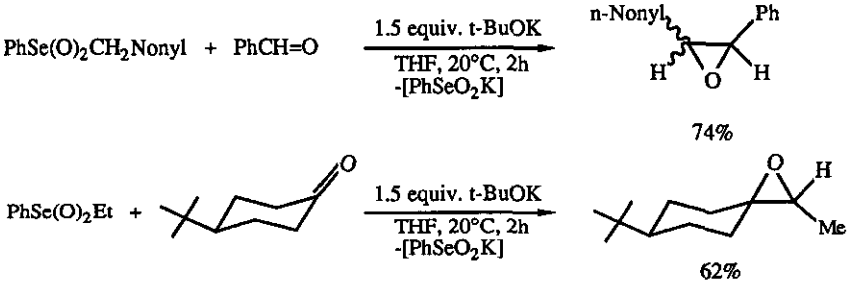
Scheme 6.



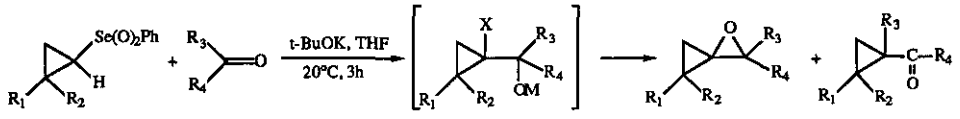
Conditions	$PhSe(O)_2Me$	$PhSe(O)_2R$ R = 1-Dec	$PhSe(O)_2R$ R = 2-Dec		
	Yield % (h)	Yield % (h)	Yield % (5h)	Yield % (h)	Yield % (72h)
2.5 equiv. mCPBA CH_2Cl_2	40 (2)	68 (5)	0	R=Me 37 (24)	-
2.5 equiv. CF_3CO_3H, CH_2Cl_2	70 (0.5)	70 (1)	0	-	-
1.5 equiv. aq. $KMnO_4$, CH_2Cl_2	75 (0.5)	low (48)	0	R=Me 70 (24) R=H 82 (5)	0
1 equiv. $PhSeO_2H$, 10 equiv. H_2O, CF_3CH_2OH	50 (5)	83 (5)	0	R=Me 68 (6)	-

Only few epoxides have been prepared from primary alkylselenones [7a] (Scheme 7) but the reaction proved particularly suitable for the synthesis of oxaspiropentanes from ketones (Scheme 8 entries a-d). It is a good substitute to related reactions which use cyclopropylidenediphenylsulfurane [13] or 1-bromo-1-lithiocyclopropane [14] since the by-product (potassium phenylseleninate) is water soluble and more easily separated from the oxaspiropentane than the diphenylsulfide produced in the former case and because the parent compounds are not readily available in the second one due to the difficult synthesis of 1,1-dibromocyclopropane, the required starting material.

Scheme 7.



Scheme 8.



	R_1	R_2	R_3	R_4	overall yield	(epoxide / ketone ratio)
a	H	H	Me	n-Hex	92	(100 / 0)
b	H	H	Me	Ph	98	(100 / 0)
c	H	H	CH_2 - $(CH_2)_4$ - CH_2		98	(100 / 0)
d	H	H	$(CH_2)_2CH(t\text{-}Bu)\text{-}(CH_2)_2$		94	(100 / 0)
e	H	H	H	Ph	70	(50 / 50)
f	Me	Me	H	Ph	74	(75 / 25)
g	Me	Me	H	n-Hex	45	(30 / 70)

Aldehydes also react under the above mentioned conditions with 1-metallo-1-phenylselenonylcyclopropanes but now oxaspiropentanes and cyclopropylketones are concomitantly produced (Scheme 8 e-g). This behaviour is different from the one of bromo derivatives which exclusively lead [14] to the cyclopropylketones and of sulfur ylides which exclusively produce [13] oxaspiropentanes.

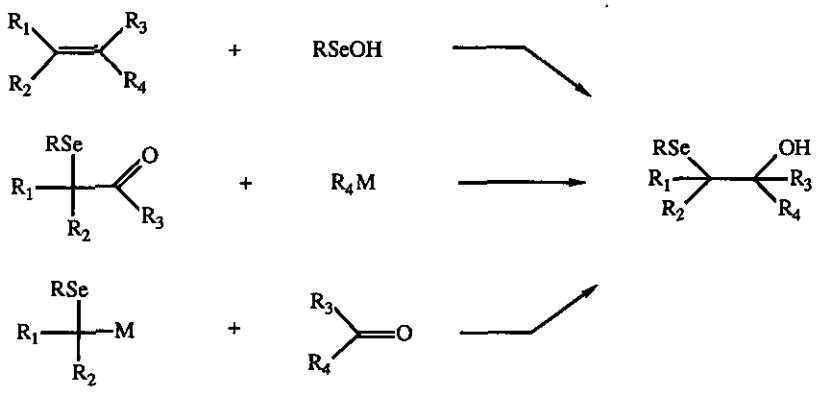
B. Synthesis of epoxides from β-hydroxyalkylselenides.

Otherwise, epoxides have been produced on reaction of β-hydroxyalkylselenonium salts and β-hydroxyalkylselenones (readily prepared from β-hydroxyalkylselenides by alkylation [4-6] or by oxidation [12]) with bases (Scheme 2b).

β-Hydroxyalkylselenides are available as shown in the Scheme 9 from **(i)** olefins and electrophilic selenium reagents [1a-k,4d,5b] **(ii)** α-selenocarbonyl compounds and organometallics [5a] and **(iii)** from α-selenoalkyllithiums and carbonyl compounds [4,17-19] (Scheme 9).

Since β-hydroxyselenides can be regio- and stereoselectively transformed to epoxides (see below), it is important to have regio- and stereoselective synthesis of these derivatives. It must be however taken into account that interconverting the position of the hydroxyl and the selenyl moieties does not affect the regiochemistry of the resulting epoxides.

Scheme 9.



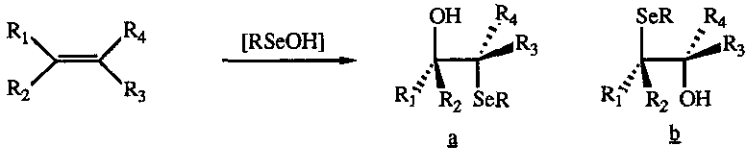
1. Synthesis of β-hydroxyalkylselenides.

a. From olefins.

β-Hydroxyalkylselenides have been stereoselectively prepared (Scheme 10) by hydrolysis of β-halogenoalkylselenides[5b] (H_2O, CF_3CH_2OH or H_2O, DMF or H_2O, SiO_2, 20°C) or of β-acetoxy- [1a-k,15ab] or β-trifluoroacetoxy- [1a-k,15c] alkylselenides (aq. KOH). These compounds have, in fact, been prepared from olefins and selenenyl halides in chlorinated solvents [1a-k,5b], in acetic acid [1a-k,15a,b] or in the presence of silver trifluoroacetate [1a-k,15c] respectively. β-Hydroxyalkylselenides can be synthesized even more rapidly by addition [4d,16] of selenenic acids to olefins (Scheme 10). These unstable reagents which must be prepared in situ by dismutation of a mixture of diselenides and seleninic acids [2d,16a] or by reduction of the latter with hypophosphorous acid [4d,16b] or hydrazine [16c,d], react in a completely different manner than analogous sulfenic acids which instead lead to sulfoxides [8b]. Selected examples are gathered in the Scheme 10. All these reactions provide β-hydroxyalkylselenides resulting from the formal anti addition of the hydroxyl and selenyl moieties across the C,C double bond of the olefin, the selenenyl unit exhibiting a high tendency to be attached to the least substituted of the two carbon atoms (Scheme 10).

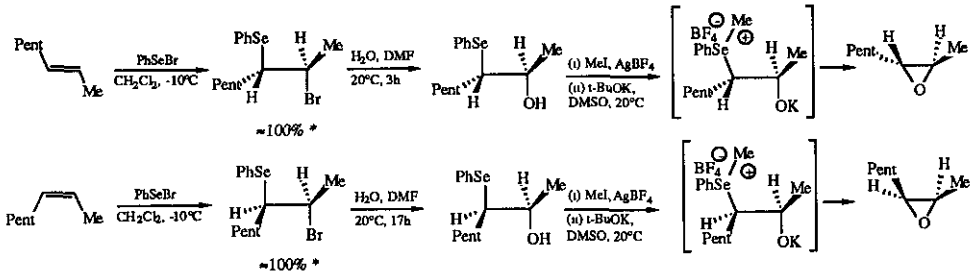
Further activation of the selenyl moiety provides (Scheme 11) epoxides whose stereochemistry is the same as the one obtained directly from the same olefins and peracids or via a two steps sequence which involves the addition of the hypohalous acid and treatment of the resulting halohydrin with a base [20a-c]. The latter synthesis and the one involving electrophilic selenium species should lead to the epoxidation of the most hindered face of the olefinic compound. There is however a striking difference between these two different syntheses since it is well established that hypohalous acids and related reagents react [20b] on the more alkyl substituted C,C double bonds whereas it has been described[5b] that the selenenyl halides react on the least substituted ones and therefore one could expect (although it has not yet been achieved) a different chemoselectivity in the epoxide synthesis from the same polyolefinic compounds.

Scheme 10.



R_1	R_2	R_3	R_4	R	Conditions	Yield % (a/b ratio)	ref
n-Hex	H	H	H	Ph	(i) 1.2 equiv. PhSeBr, 1.4 equiv CF_3CO_2Ag ether -10°C to +10°C, 2h (ii) $NaHCO_3$, MeOH, 20°C, 3h	87 (mixture)	15c
n-Oct	H	H	H	Ph	(i) 1 equiv. PhSeBr, CH_2Cl_2, 20°C, 1h		
					(ii) H_2O, CF_3CH_2OH, 20°C, 2h	74 (99 / 1)	5b
					or (ii) H_2O, DMF, 20°C, 72h	68 (91 / 8)	5b
					or (ii) SiO_2 (Merck 7747) CH_2Cl_2, 20°C, 18h	72 (-)	5b
					1.5 equiv. $PhSeO_2H$, 2.5 equiv. aq. H_3PO_2, THF, 20°C, 1.5h	91 (68 / 32)	5b
n-Oct	H	H	H	Me	(i) MeSeBr, CH_2Cl_2, 20°C, 1h (ii) H_2O, DMF, 20°C, 74h	63 (69 / 31)	5b
					1.5 equiv. $MeSeO_2H$, 2.5 equiv. H_3PO_2, THF, 20°C, 2.5h	79 (56 / 44)	4d
Ph	H	H	H	Ph	1.5 equiv. $MeSeO_2H$, 2.5 equiv. H_3PO_2, THF, 20°C, 2h	92 (100 / 0)	4d
Ph	H	H	H	Me	1.5 equiv. $MeSeO_2H$, 2.5 equiv. H_3PO_2, THF, 20°C, 2h	88 (100 / 0)	4d
Pent	H	H	Me	Me	1.5 equiv. $MeSeO_2H$, 2.5 equiv. H_3PO_2, THF, 20°C, 3.5h	78 (35 / 65)	4d
Pent	H	Me	H	Me	1.5 equiv. $MeSeO_2H$, 2.5 equiv. H_3PO_2, THF, 20°C, 3h	76 (30 / 70)	4d
n-Pr	H	H	n-Pr	Ph	1 equiv. $(PhSe)_2$, 1 equiv. $PhSeO_2H$, 20°C	84 (-)	2d
Me	Me	n-Bu	H	H	1 equiv. $(PhSe)_2$, 1 equiv. $PhSeO_2H$, 20°C	- - (85 / 15)	2d
					1 equiv. $(PhSe)_2$, 1 equiv. $PhSeO_2H$, $MgSO_4$, 20°C	- - (100 / 0)	2d
Me	Me	3-Me-Pent	H	Ph	1.5 equiv. $MeSeO_2H$, 2.5 equiv H_3PO_2, THF, 20°C, 1h	86 (100 / 0)	4d
Me	Me	3-Me-Pent	H	Me	1.5 equiv. $MeSeO_2H$, 2.5 equiv H_3PO_2, THF, 20°C, 1.5h	80 (100/0)	4d

Scheme 11.

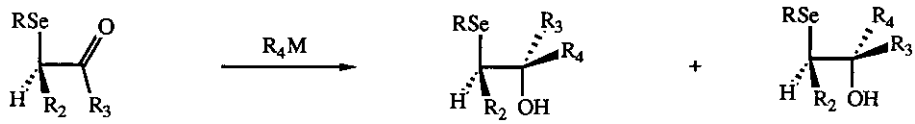


* the regioisomer is also formed.

b. From α-selenocarbonyl compounds.

β-Hydroxyalkylselenides have been also conveniently prepared from α-selenocarbonyl compounds [1b-l,5a,21] and hydrides or organometallics. The reaction is best achieved [1e,f,5a] with lithium aluminum hydride in ether or with Grignard reagents in ether or THF (Scheme 12). The latter react efficiently [5a] with α-selenoaldehydes but lead to very poor yields of the desired compounds from α-selenoketones (Scheme 12 entry f).These reagents have to be preferred to sodium borohydride in ethanol and alkyllithiums which effect at various level the deselenylation of the starting material.[1e,f,5a]

Scheme 12.

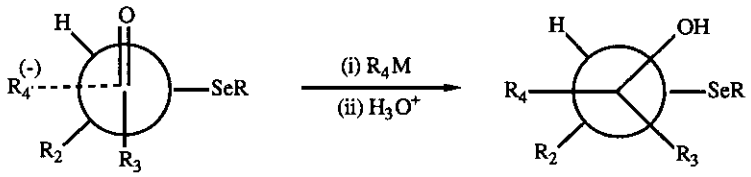


a b

	R_2	R_3	R	R_4	Conditions	Yield % (a / b) ratio
a	n-Pent	H	Ph	H	$AlLiH_4$, ether, -15°C	60
b	n-Dec	H	Me	Me	MeMgBr, ether, -110°C, 2h, -78°C, 1h	75
c	n-Dec	H	Me	n-Dec	n-DecMgBr, ether, -110°C, 2h, -78°C, 1h	68 (85 / 15)
d	n-Pent	H	Ph	n-Dec	n-DecMgBr, ether, -110°C, 2h, -78°C, 1h	65 (94 / 6)
e	n-Non	n-Dec	Ph	H	$AlLiH_4$, ether, -15°C	60 (16 / 84)
f	H	Me	Ph	n-Dec	n-DecMgBr, ether, -110°C, 2h, -78°C, 1h	24

The reaction is reasonably stereoselective and delivers β-hydroxyalkylselenides whose stereochemistry can be predicted on the base of Felkin's model [22] in which the separation between the selenyl group and the incoming organometallic is the greatest (Scheme 13). The highest diastereoselection observed with phenylseleno derivatives (Scheme 12 compare entries c and d) also fits in the Felkin's predictions [22] since the more polarisable phenylseleno group possesses a higher propensity than the methylseleno one to delocalize the charge.

Scheme 13.

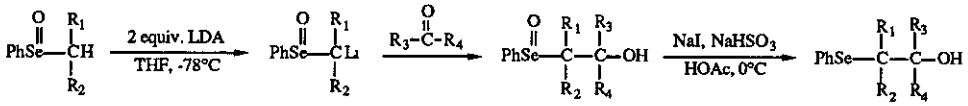


The above mentioned reaction parallels in fact the one implying α-chloroketones and organometallics which was used purposely by Cornforth [23] for the first stereoselective synthesis of squalene. Our app.roach, however,offers the definite advantage over the one implying halogenoketones [20] to be completely regioselective since α-seleno carbonyl compounds are regioselectively available [21b] from α-selenoalkylithiums and carboxylic acid derivatives.

c. From carbonyl compounds..

These syntheses involve the reaction of α-selenoalkylmetals [17,18,24-26] with aldehydes and ketones and allow the concomitant formation of a new carbon-carbon bond which will be part of the three membered heterocycle. Although the most straighforward route would imply the reaction of α-selenoalkyllithiums with carbonyl compounds, an alternative procedure has been devised which involves [24] the reaction of α-selenoxyalkylithiums (readily obtained by metalation of the corresponding selenoxides [1a-k,24]) with carbonyl compounds but requires, in a further step, the reduction [24b] of the β-hydroxyalkylselenoxides (Scheme 14). This two steps sequence has been proposed [24b] in order to overcome the difficulties encountered *,[1f,j,l] for the synthesis of α-selenoalkyllithiums by direct metalation of the corresponding selenides.

Scheme 14.



	R_1	R_2	R_3	R_4		
a	H	H	CH_2-$(CH_2)_3$-CH_2			75% overall
b	H	$(CH_2)_2Ph$	Me	Me		88% overall
c	Me	Me	CH_2-$(CH_2)_8$-CH_2			82% overall
d	H	H	CH_2-CH_2-C(Me)Ph		92%	
e	H	$CHMe_2$	CH_2-CH_2-cyclohex-2-enyl		71%	
f	Me	Me	CH_2-CH_2-C(Me)Ph		39%	

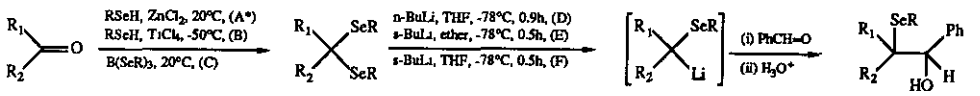
In fact, the far more versatile route to β-hydroxyalkylselenides still remains the direct reaction of α-selenoalkyllithiums with carbonyl compounds. It takes advantage of (i) the great availability [1c,d,f,j,l,4,17,18] of these species from the corresponding selenoacetals and alkyllithiums and (ii) their exceptional nucleophilicity [1f,j,l,4b,g,6b] towards carbonyl compounds which proved better than the one of α-selenoxyalkyllithiums [24c,d]. It offers the possibility to synthesize a large variety of β-hydroxyalkylselenides including methylseleno derivatives which are not available by the selenoxy route but which proved particularly good precursors of selenonium salts and in consequence of epoxides.

On the synthesis of α-selenoalkyllithiums. The key step of the above process is without contest the synthesis of α-selenoalkyllithiums which has been efficiently achieved by cleavage of one of the C-Se bond of phenyl- and methylselenoacetals [27], by butyllithiums [1c,d,f,j,l,4,17,18]. Under standard conditions the reactions are performed at -78°C (the temperature at which the α-selenoalkyllithiums are stable for more than 5h) with n-butyllithium in THF-hexane (method D) or sec-butyllithium in ether-hexane * (method E). They usually allow, in less than 2h, the quantitative synthesis of a large variety of α-phenylseleno- and α-methylselenoalkyllithiums whose carbanionic center is unsubstituted, monoalkyl- or even dialkyl-substituted (Scheme 15). Cycloalkyl- and arylsubstituted derivatives are available as well. As a general trend, all the factors which allow the stabilization of the carbanionic center will favor the reaction. Thus, phenylselenoacetals react more rapidely than their methylseleno analogues and selenoalkyllitiums whose carbanionic center is part of a three membered cycle or aryl substituted derivatives are more readily obtained [18c-e] than the dialkyl substituted ones.

The presence of bulky groups around the reactive site has no marked effect on the reactivity of selenoacetals derived from aldehydes but dramatically lowers the reaction rate of those derived from ketones (i.e. adamantanone, diisopropyl and di-n-hexylketone) especially if the reaction is carried out with n-butyllithium in THF. In these cases, the use of sec-butyllithium instead of n-butyllithium greatly enhances [18c,e] it (Scheme 15). The required selenoacetals have been obtained, with the exception of the parent compounds 4b,[17b] and the selenoacetals derived from cyclopropanones,[11,18c] by selenoacetalization [27] of aldehydes and ketones with phenyl- and methylselenol in the presence of a Lewis acid [$ZnCl_2$, CCl_4, (method A) or $TiCl_4$, CH_2Cl_2 (method B) or with tri-selenoborane (method C)]. The reaction is usually carried out at 20°C with zinc chloride (0.5 equiv. versus the carbonyl compound) and delivers rapidly (< 3h) and in quite good yield phenyl- and methylselenoacetals derived from aliphatic aldehydes and ketones and cyclic ketones as well (Scheme 15). It is clearly more difficult to achieve [27] with hindered ketones such as adamantanone and diisopropylketone and this is particularly the case in the phenylseleno series.

* The metalation of selenides is restricted to methyl phenyl selenide [17a,b] and to those selenides which bear a group able to stabilize the carbanionic center on the resulting organometallic such as a phenyl, [25] vinyl or alkynyl [26] moiety.

Scheme 15.



RSeCH$_2$Li

Me 80(§); 80(D); 82(E)
Ph 80 (§); 82(D)

RSeCH(Me)Li

Me 91(A); 80(D)
Ph 90 (A); 70(D)

RSeCH(n-Hex)Li

Me 72(A); 84(D); 82(E)
Ph 79(A); 89(D); 74(E)

RSeCH(t-Bu)Li

Me 90(A); 82(D)
Ph 90(A); 92(D

RSeC(Me$_2$)Li

Me 90(A); 75(D); 80(E)
Ph 85(A); 94(D); 83(E)

RSeC(Me)(n-Hex)Li

Me 77(A); 90(D, 2h)
Ph 80(A); 78(D)

RSeC(Me)(t-Bu)Li

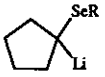
Me 81(A); 32(D); 77(D, 2h)
Ph 32(A); 59(D)

RSeC(n-Hex)$_2$Li

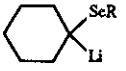
Me 66(A); 17(D)
93(D, 4h); 9(F)
Ph 16(A); 47(D)

Me 91(D); 68(E)
Ph 80(D)

Me 89(A); 87(D)
Ph 84(A); 90(D)



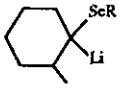
Me 87(A); 82(D)
Ph 81(A); 91(D)



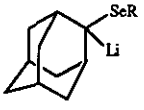
Me 91(A); 87(D, 2h)
Ph 81(A); 88(D)

RSeC(i-Pr)$_2$Li

Me 16(A); 69(B); 77(D, 2h)
Ph 0(A); 0(B)



Me 64(A); 25(D); 78(E); 87(F)
Ph 62(A); 55(D, 4h); 79(E)



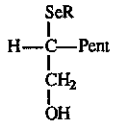
Me 88(A); 0(D); 81(F)
Ph 27(A)

The following informations are given : nature of the substituent, yield in the selenoacetal recursor of the a-selenoalkyllithium, yield in the b-hydroxylkylselenide reultung from the further reaction with benzaldehyde. If not otherwise stated, the reactions are performed under the A and D methods inless than 3h and 0.2h respectively.
(§) The acetals were obtained by reaction of the corresponding selenolate on diiodomethane.

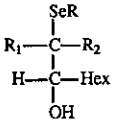
On the reactivity of α-selenoalkyllithiums. α-Phenylseleno- and α-methylselenoalkyllithiums proved particularly nucleophilic species which react already at -78°C with a large variety of aldehydes and ketones[1b-k,4,6,11,17,18] to deliver the corresponding β-hydroxyalkylselenides in good to excellent yields. The reaction is usually carried out in THF or ether and generally at a temperature lower than -60°C since the decomposition of these organometallics often occurs around -50°C(Schemes 16,17,18,19,20). Both phenyl- and methylseleno derivatives behave usually almost similarly except with particularly hindered [4b,g,l,m] or enolisable [4b] carbonyl compounds(Schemes 17,18) for which methylseleno derivatives proved far more nucleophilic in THF. Interestingly, the use of ether in place of THF tends to slightly increase [4g,l,m] the nucleophilicity of methylseleno compounds but dramatically increase [4g,l,m] the one of their phenylseleno analogues (Scheme 17) .

* sec-Butyllithium has been replaced in some cases by tert-butyllithium under the conditions (method G) without special advantages.

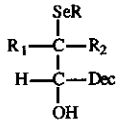
Scheme 16.



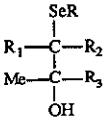
58 (Me, D) 78 (Ph, D) [11b]



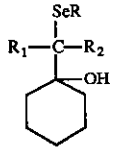
R_1	R_2		
H	n-Hex	75 (Ph, D)	[18a]
H	n-Hex	82 (Me, D)	[18a]
H	Et	50 (Ph, D)	[4a]
Me	Et	82 (Me, D)	[4b]
-$(CH_2)_5$-		76 (Me, D)	[4b]
H	t-Bu	79 (Me, D)	[41]
Me	t-Bu	57 (Me, D or E)	[41]



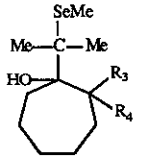
R_1	R_2		
H	H	71 (Ph, D)	[18a]
H	H	71 (Me, D)	[18a]
H	Me	80 (Ph, D)	[18a]
$(CH_3)_3$		90 (Ph, D)	[18b]
$(CH_3)_3$		71 (Me, D)	[18b]
$(CH_2)_2CH$(n-Pent)		67 (Me, D)	[4h]
CH_2-CH_2		67 (Me, D)	[4h]



R_1	R_2	R_3		
H	tBu	Hex	75 (Ph, D)	[18a]
H	tBu	Hex	44 (Me, E)	[41]
Me	tBu	Hex	9 (Me, E)	[41]
$(CH_2)_3$		Non	78 (Me, D)	[4n]
$(CH_2)_2$		Non	54 (Me, D)	[18c]
$(CH_2)_2$		Non	70 (Me, G)	[18c]
Me	Me	Hex	79 (Ph, E)	[4m]
Me	Me	Hex	73 (Me, E)	[4m]
Me	Me	Non	63 (Me, D)	[18b]

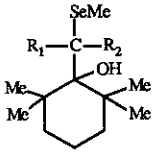


R_1	R_2		
H	Me	94 (Me, D)	[4b]
H	Hex	60 (Me, D)	[4b]
Me	Et	60 (Me, D)	[4b]
$(CH_2)_5$		70 (Ph, E)	[19g]
Me	Me	78 (Ph, D)	[3a]

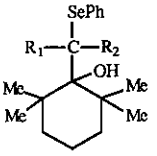


R_3	R_4		
H	H	64 (E)	[19g]
H	Me	64 (E)	[19g]
Me	Me	64 (E)	[19g]
$(CH_2)_4$		88 (E)	[19g]

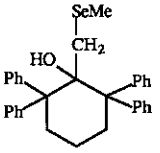
Scheme 17.



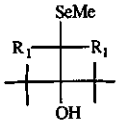
R_1	R_2			
H	H	83 (D);	87 (E)	[4g,1]
H	Me	83 (D);	85 (E)	[4g,1]
Me	Me	77 (D);	85 (E)	[4g,1]



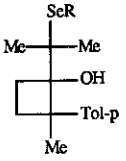
R_1	R_2			
H	H	22 (D);	85 (E)	[4g,1]
H	Me	5 (D);	63 (E)	[4g,1]
Me	H	0 (D);	60 (E)	[4g,1]



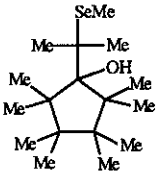
O (D, F or G) [4m]



R_1			
H	81 (F)		[4m]
Me	76 (G, -45°C)		[4m]



O (Me, D); 66 (Me, E) [6b]
O (Ph, D); 49 (Ph, E) [6b]

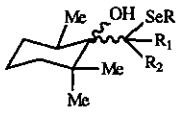


23 (E) [28a]

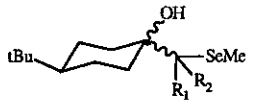
Method D : n-BuLi, THF-hexane, -78°C. Method E : s-BuLi, ether-hexane, -78°C.
Method F : s-BuLi, THF-hexane, -78°C. Method G : t-BuLi, ether-hexane, -78°C.

Scheme 18.

[a : axial alcohol, b : equatorial alcohol]

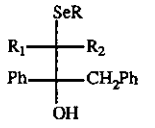


R_1	R_2	Yield [a / b]	
H	H	92 [18/82]	(Me, D) [4g,l]
H	H	85 [31/69]	(Me, G) [4g,l]
H	Me	85 [95/05]	(Me, D or G) [4g,l]
Me	Me	48 [33/67]	(Me, D) [4g,l]
Me	Me	85 [95/05]	(Me, G) [4g,l]
Me	Me	00	(Ph, D) [4g,l]
Me	Me	84 [95/05]	(Ph, G) [4g,l]

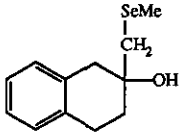


R_1	R_2	Yield [a / b]	
H	H	85 [75/25]	(D) [4k,l]
H	H	75 [69/31]	(G) [4k,l]
H	Me	70 [90/10]	(D) [4k,l]
H	Me	79 [90/10]	(G) [4k,l]
Me	Me	75 [100/00]	(D or G) [4k,l]

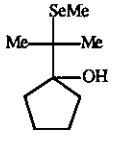
Scheme 19.



R_1	R_2		
H	H	82	(Ph, D) [4a]
H	Me	69	(Ph, D) [4a] 88 (Me, D) [4b]
H	n-Hex	75	Me D) 80 (Me, G) [4m]
Me	Me	88	(Me, D) [4b]
(CH_2)		56	(Me, D) [4a] 70 (Me, G) [18a]
$(CH_2)_3$		68	(Me, D) [18f]

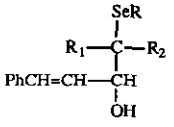


44 (D) [4m]

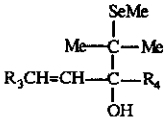


45 (D) [4m]

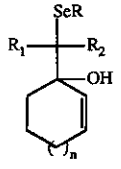
Scheme 20.



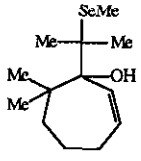
R_1	R_2		
H	Me	90	(Me, D) [4e]
H	Me	66	(Ph, D) [19g]
H	n-Hex	68	(Ph, D) [4e]
Me	Me	85	(Me, D) [4e]
Me	Me	78	(Ph, D) [4c]



R_3	R_4		
n-Pr	Me	74	(E) [19g]
n-Pr	Et	74	(E) [19g]
H	Me	55	(D) [4c]
Me	Me	45	(D) [4c]
Ph	Ph	21	(D) [4c]



n	R_1	R_2		
1	H	n-Hex	64	(Me, D) [4e]
1	Me	Me	55	(Me, D) [4c]
1	Me	Me	83	(Ph, E) [19c]
2	Me	Me	57	(Me, E) [19c]
2	Me	Me	51	(Ph, E) [19c]
7	Me	Me	54	(Me, E) [19c]



14 (D), 46 (E) [19c]

It is particularly efficient with hindered ketones such as 2,2,6-trimethylcyclohexanone (Scheme 18), 2,2,6,6,-tetramethylcyclohexanone [4g] (Scheme 17), di-tert-butyl ketone [4l,m] and even permethylcyclopentanone [28a] (Scheme 17) which all react with variously substituted α-selenoalkyllithiums including 2-methylseleno-2-propyllithiums. The reaction does not, however, take place with 2,2,6,6-tetraphenylcyclohexanone [28b] (Scheme 17), and is less efficient with highly enolisable ketones and although it proceeds efficiently for deoxybenzoin [1f,j,4b], the yields of β-hydroxyselenides derived from cyclopentanone or β-tetralone are modest [4n] (Scheme 19).

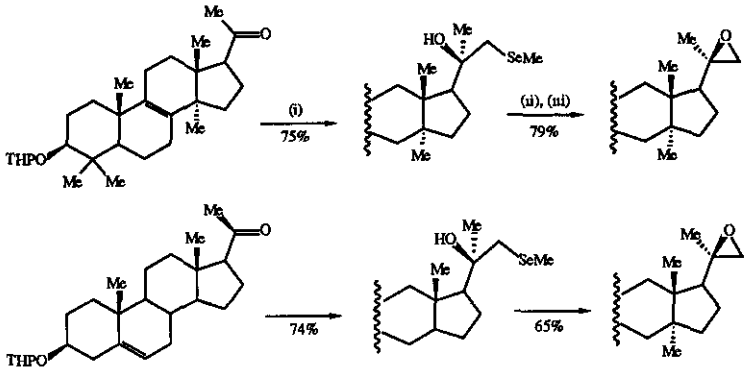
Otherwise, the reaction seems to be more sensitive to steric hindrance around the carbanionic center of the α-selenoalkyllithiums than to the one around the carbonyl group of the ketone.

α-Selenoalkyllithiums even those bearing two alkyl substituents on the carbanionic center possess a high propensity to add [4c,e] on the carbonyl group of enals and enones rather than on their carbon-carbon double bond and produce the corresponding β-hydroxy-γ-alkenylselenides in fair yields (Scheme 20). This aptitude to react at the C_1 site of enones is not observed with *all* α-hetero-substituted organometalics [1f,8,9c].

Unfortunately, the reactions involving aliphatic and aromatic aldehydes and straight chain ketones are not stereoselective whatever the solvent used (ether or THF). Even in those most favorable cases, such as that of 1-methylseleno-2,2-dimethylpropyllithium and heptanal in which well differentiated bulky groups are involved, the stereoisomeric ratio ranges from 1/1 to 3/2. Interestingly, however, diastereoisomeric mixtures of β-hydroxyalkylselenides can be often quantitatively separated [4h,l,m] by chromatography on silica gel (see below).

α-Selenoalkyllithiums react stereoselectively with rigid cyclohexanones such as 4-tert-butylcyclohexanone [4k] and 2,2,6-trimethylcyclohexanone [4g] and often lead to products resulting from an equatorial attack (Scheme 19). They also react on the less hindered face of protected pregnenolone and related steroidal ketones to produce [4j] 20R derivatives in good yield (Scheme 21).

Scheme 21.



(i) $MeSeCH_2Li$, ether-hexane, (ii) $MeSO_3F$, 0°C to 20°C, 1h, (iii) 10% aq. KOH, ether, 20°C, 16h.

2. Synthesis of epoxides from β-hydroxyalkylselenides.

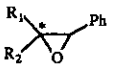
Except rare cases, which are not the subject of this review, the reaction of β-hydroxyalkylselenides with bases (KOH, t-BuOK / DMSO) does not afford the corresponding epoxides.Clearly, the selenyl moiety has to be transformed to a better leaving group (Scheme 2b). Such activation has been usually achieved by selective alkylation or oxidation of the selenyl moiety to produce respectively β-hydroxyalkylselenonium salts and β-hydroxyalkylselenones. These species have then been cyclized to epoxides by subsequent reaction with bases.

A more direct procedure in which the activation step is directly performed in a basic medium was also found. It involves the treatment of β-hydroxyalkylselenides by thallous ethoxide in chloroform.

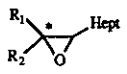
a. Synthesis of epoxides via β-hydroxyalkylselenonium salts.

This sequence proved particularly efficient when applied to the methylseleno derivatives. These compounds are more reactive [4a,b,g] towards methylating agents than their phenylseleno analogues and allow the synthesis of a large variety of β-hydroxyalkyldimethylselenonium salts, precursor of epoxides (Schemes 22, 23, 24, 25).

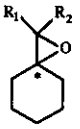
Scheme 22.



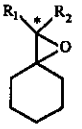
R_1	R_2		
H	H	97x72 (Ph, HxL)	[4a]
$(CH_2)_5$		67x93 (Me, IxL)	[4b]
H	Me	88x97 (Me, IxL)	[4b]
Me	Me	92x80 (Me, IxL)	[4b]



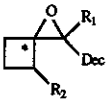
R_1	R_2		
Me	Et	90x66 (Me, IxL)	[4b]
H	n-Hept	100x88 (Me, JxM)	[4n]



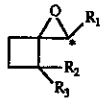
R_1	R_2		
H	n-Hex	83 (Me, KxL)	[4m]



R_1	R_2		
H	Me	94x93 (Me, IxL)	[4b]
H	n-Hex	90x72 (Me, IxL)	[4a]
Me	Et	100x86 (Me, IxL)	[4b]

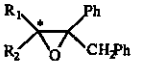


R_1	R_2		
H	Me	81 (Me, IxL)	[4b]
H	n-Pent	71 (Me, IxL)	[4h]
Me	H	70 (Me, IxN)	[4]

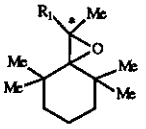


R_1	R_2	R_3		
n-Dec	H	H	65 (Me, I	
H	Me	n-Non	67 (Ph, I	

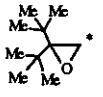
Scheme 23.



R_1	R_2		
H	H	93x46 (Ph, HxL)	[4a]
H	Me	73x51 (Ph, IxL)	[4a]
H	Me	73x98 (Me, JxL)	[4b]
Me	Me	88x90 (Me, IxL)	[4b]

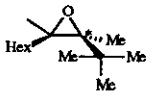


R_1		
Me	98 (Me, KxN)	[4g]
n-Hex	92 (Me, KxN)	[4g]



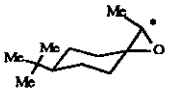
94 (Me, HxN) [4l]

Scheme 24.

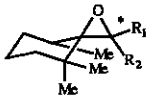


99 (Me, IxN) [4m]

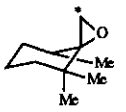
R_1	R_2		
H	Me	65 (Me, IxN)	[4m]
Me	Me	91 (Me, KxM)	[4k]



65 (Me, IxN) [4n]



R_1	R_2			
H	H	95 (Me, KxN)	96 (Me, JxM)	[4g]
H	Me	99 (Me, KxN)	89 (Me, JxM)	[4g]
Me	Me	94 (Me, KxN)	100 (Me, JxN)	[4g]
CD_3	CD_3	82 (Me, KxN)	[4l]	



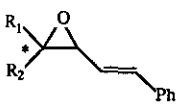
95 (Me, KxN) [4g]

* refers to the place where the seleno moiety was attached on the β-hydroxyalkylselenide.

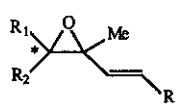
Method H : $AgBF_4$, MeI, CH_2Cl_2, 20°C. Method I : MeI, neat or CH_2Cl_2, 20°C. Method J : Me_2SO_4, neat or CH_2Cl_2, 20°C. Method K : CF_3SO_3Me, ether, -78°C or -20°C to 20°C. Method L : t-BuOK, DMSO, 20°C. Method M : KOH (50% aq.), CH_2Cl_2, 20°C. Method N : KOH (10% aq.), ether, 20°C.

In the methylseleno series, the alkylation is usually performed at 20°C with methyl iodide [4b,g] (method I) or dimethyl sulfate [4b,g] (method J) preferentially neat or in methylenedichloride and is dramatically slowered down if instead carried out in diethyl ether [4l,n]. It is interesting to notice[4l,n] that β-hydroxyalkylmethylselenides are more easily alkylated than the corresponding alkyl methyl selenides.
Differently substituted β-hydroxyalkyldimethylselenonium salts including those fully alkyl-substituted on the carbon bearing the hydroxyl and the seleno moieties have been produced [1b,f,4c,e,g-j,l,m] almost quantitatively and usually in less than 5hrs (schemes 22, 23, 24, 25).

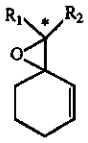
Scheme 25.



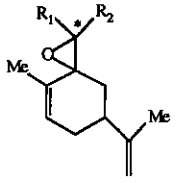
R_1	R_2		
Me	H	90x94 (Me, IxL) [4c]	
Hex	H	96 (Me, JxL) [4e]	
Me	Me	80 (Me, IxN) [4e]	
Me	Et	86 (Me, IxN) [4e]	



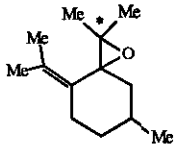
R	R_1	R_2	
Ph	H	H	75 (Me, IxL) [4c]
Ph	Me	Me	89 (Me, IxL) [4e]
Me	H	Hex	40 (Me, IxN) [4e]
Me	Me	Me	50 (Me, IxN) [4e]



R_1	R_2		
H	Hex	77 (Me, IxL) [4e]	
Me	Me	95 (Me, JxL) [4e]	



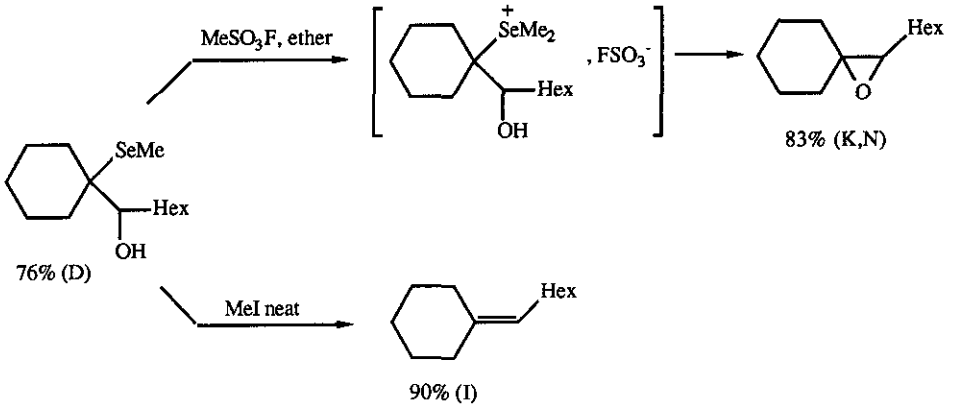
76 (Me, IxL) [4c]



98 (Me, IxL) [4c]

Particularly hindered β-hydroxyalkylselenides derived from 2,2,6-trimethyl- or 2,2,6,6-tetramethylcyclohexanone which do not react [4g] properly under the above mentioned conditions are efficiently methylated [4g] with magic methyl (methyl fluorosulfonate, method K) (Scheme 23). The reaction is so fast that it can be conducted in ether even at very low temperature (-78°C or -20°C then heating to 20°C) and provides [4g] the corresponding β-hydroxyalkylselenonium fluoroborates in almost quantitative yield. It also allows [4n] the almost quantitative synthesis of the selenonium salt derived from the β-hydroxyalkylselenide shown in the Scheme 26 which leads instead to heptylidenecyclohexane when reacted [4b] with methyl iodide (method I).

Scheme 26.



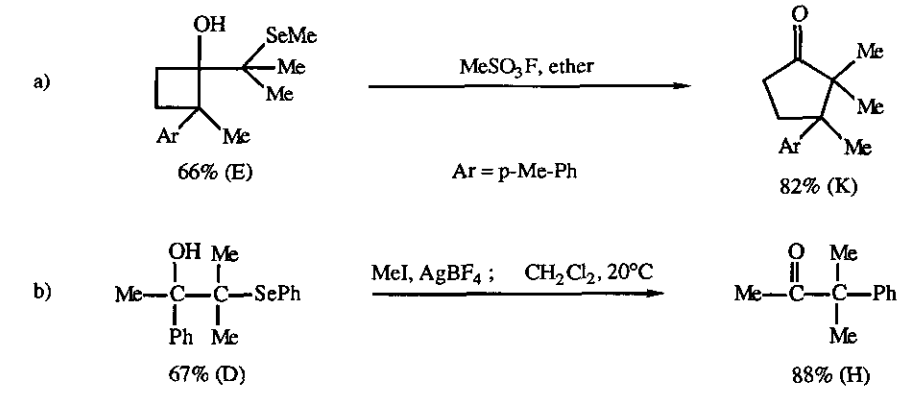
However, β-hydroxyalkylselenides derived from cyclobutanones, especially the α-aryl substituted ones, and α-selenoalkyllithiums whose carbanionic center is fully alkyl-substituted, are prone to rearrange and directly lead to cyclopentanones rather than to the selenonium salts [6b,18h] whatever the conditions used (Scheme 27a). This reaction has been successfully used for an original synthesis of cuparenone [6b].

β-Hydroxyalkylselenonium salts are usually stable compounds which do not decompose rapidly even when heated [19a]. Those derived from 2,2,6-trimethyl- and 2,2,6,6-tetramethylcyclohexanone and 2-methylseleno-2-propyllithium are unstable and rearrange [4g] on heating around 60°C or by simple dissolution in dimethylsulfoxide or in methylenedichloride and lead to a mixture of the ring enlarged cycloheptanones and allylic alcohols (Scheme 28 entries a,c,f). They are however stable at 20°C in ether and have been further successfully transformed to the corresponding epoxides (Scheme 28 entries d,g). This rearrangement is strickly limited to those hindered derivatives whose carbon bearing the selenyl moiety is fully substituted and does not for example take place with related monoalkyl-substituted derivatives [19a].

Alkylation of β-hydroxyalkylphenylselenides is much more difficult and, for example, those possessing a phenylseleno moiety can be alkylated with dimethyl sulfate [4a] (method J) but at around 80°C. The methylation is best achieved at room temperature in methylene dichloride with triethyloxonium tetrafluoroborate [1b] or with silver tetrafluoroborate [4a,h] (method H). It delivers [4a,h] the β-hydroxyalkylselenonium tetrafluoroborate in very good yield whether the carbon bearing the seleno moiety is unsubstituted or monoalkyl substituted (schemes 22, 23).

The reaction proceeds differently with dialkyl-substituted compounds which instead lead to ketones resulting from the migration of one of the groups from the carbon bearing the hydrogen to the carbon where the phenylseleno moiety was attached [4a] (Scheme 27b). It is unclear at present if the alkylation effectively took place or if rather silver tetrafluoroborate has directly reacted on the β-hydroxyalkylphenylselenide. It was, in fact, found [19a] (later on) that this rearrangement occurs even if methyl iodide is excluded and is rather general since it also proceeds with similarly substituted methylseleno analogues. *The different results described above clearly show that methylseleno derivatives are by far superior to phenylseleno ones for the synthesis of epoxides since in the former series the alkylation reaction is not only easier but also more general..*

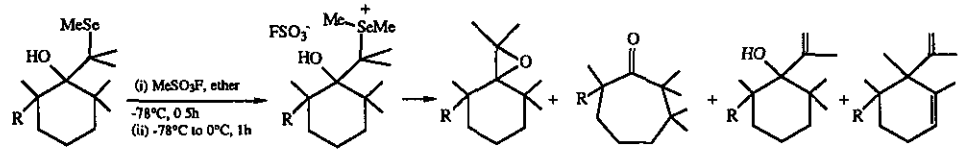
Scheme 27.



The last step requires the reaction of the above mentioned salts with a base. The reaction has been achieved under various basic conditions such as (i) potassium tert-butoxide in dimethylsulfoxide [4a-c,e] (method L), (ii) 50% aqueous potassium hydroxide and methylenedichloride [4l], the selenonium salt playing the role of phase

transfer catalyst (method M) or under similar conditions but in the presence of a tetraalkylammonium salt (method M) or (iii) with 10% aqueous potassium hydroxide and ether [4e,g,h,l-n,18d] (method N). Generally, all these conditions allow the synthesis of differently substituted epoxides [4,18d] such as terminal-, α,α-, α,β-di-, tri- and tetra-substituted epoxides including oxaspiro-hexanes, -heptanes and -octanes (Schemes 22, 23, 24) as well as vinyl oxiranes (Scheme 25). Method N (10% aq. KOH, ether) proved however in most of the cases the more suitable owing to its generality and its simplicity. For example, it allows the almost quantitative synthesis of the particularly hindered epoxide derived from 2,2,6,6-tetramethylcyclohexanone and 2-methylseleno-2-propyllithium, whereas the corresponding selenonium salt instead produces an allyl alcohol when reacted with potassium tert-butoxide in dimethyl sulfoxide (method L, scheme 28 entry b) or to the ring enlarged ketone on heating [19a] the magnesium alkoxide in methylene dichloride (Scheme 28 entry e).

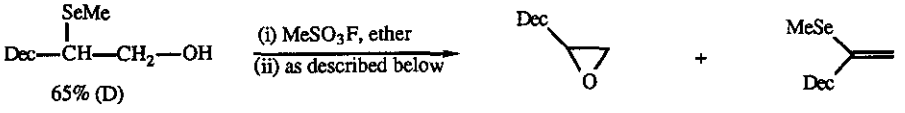
Scheme 28.



a	R=Me	DMSO, 20°C, 0.9h	90%	-	20	80	-
b		1 equiv. t-BuOK, DMSO, 20°C	90%	-	-	100	-
c		CH_2Cl_2, 20°C, 0.3h	44%	-	66	-	34
d		10% aq. KOH, ether, 0°C, 1h	94%	100	-	-	-
e		(i) MeMgBr, Et_2O, -78°C, (ii) CH_2Cl_2, 20°C	95%	-	100	-	-
f	R=H	CH_2Cl_2, 20°C, 0.3h	95%	-	100	-	-
g		10% aq. KOH, ether, 0°C, 1h	95%	100	-	-	-

Method N proved [4l,m] much better than method L, M or aqueous potassium carbonate in ether for the synthesis of 1,2-oxidododecene from dimethylselenonium-2-(1-hydroxy)dodecylmethylfluorosulfonate and minimize the amount of 2-methylseleno-1-dodecene concomitantly formed (Scheme 29). However for this specific case best results have been obtained [4l,m] when the reaction were carried out in pentane (Scheme 29 entry d).

Scheme 29.



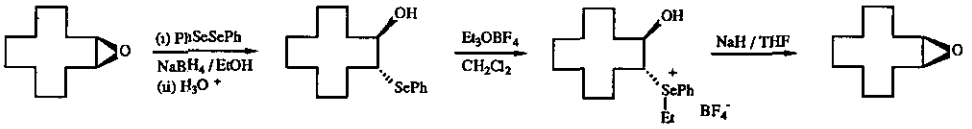
a	50% aq. KOH / CH_2Cl_2 (M)	5%	45%
b	aq. K_2CO_3 / ether	65%	30%
c	10% aq. KOH / ether	85%	15%
d	10% aq. KOH / pentane	78%	3%

Unfortunately, we have been unable [18h] to synthesize the particularly strained oxaspiropentanes from the 1-dimethylselenoniumcyclopropylcarbinols. Products resulting from a methyl transfer from the selenium to the oxygen, cyclopropenecarbinols resulting from an elimination rather than a substitution reaction as well as several unidentified compounds are instead produced [18h].

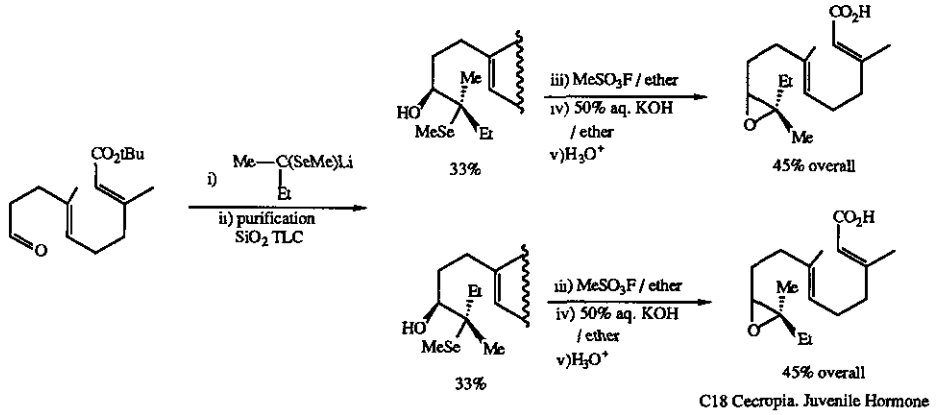
The stereochemistry of this process has been investigated [1a,4d,h,n,5a,b]. Diastereoisomerically pure β-hydroxyalkylselenides (i) synthesized directly by ring opening of stereoisomerically pure epoxides with selenolates (Scheme 30) [1a,18a,b,29] or by addition of the selenenyl and hydroxyl moiety on olefins [4d,5b,16b]

(Scheme 11) or (ii) resulting from the separation of diastereoisomeric mixtures of β-hydroxyalkylselenides [4n] (Schemes 24, 31) produce completely stereospecifically the corresponding epoxides.

Scheme 30.



Scheme 31.



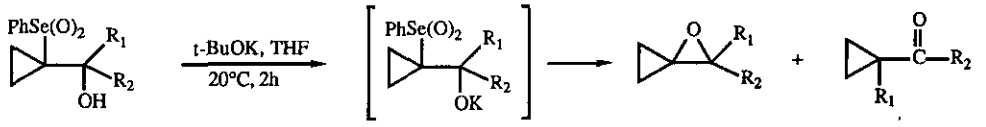
C18 Cecropia. Juvenile Hormone

The reaction occurs with net inversion of the configuration at the substituted carbon whether it is mono-alkyl [1a,4d,n,5b,6a] (Schemes 11,30) or dialkyl-substituted [4n] (Schemes 24,31) and therefore proceeds without concomitant C,C bond cleavage on the betaïne intermediate which would have led after the recombination of the resulting selenonium ylide and carbonyl compound to a diastereoisomeric mixture of epoxide. The latter process has been found to take place indeed on some related sulfoxonium betaïnes [30].

b. Synthesis of epoxides via β-hydroxyalkylselenones.

As already mentioned the transformation of β–hydroxyalkylselenides to their selenonium salts allow the synthesis of almost all the different alkyl-, alkenyl- or aryl-substituted epoxides but fails to produce oxaspiropentanes [1,8h]. These are however available [7b] on reaction of the corresponding β–hydroxyalkylselenones with a base (t-BuOK, THF, 20°C). The reaction is particularly clean with those compounds derived from ketones (Scheme 32a) but lead to a mixture of oxaspiropentane and cyclopropylketone with those derived from aldehydes (Scheme 32b).

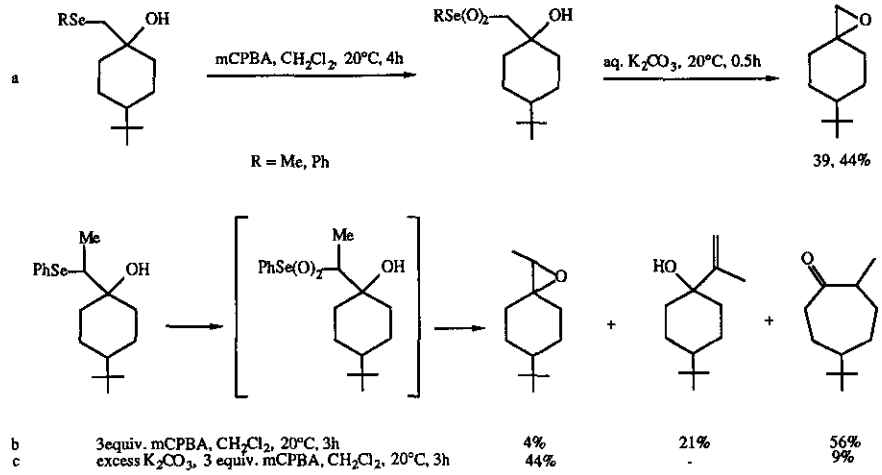
Scheme 32.



a	R_1 = Me	R_2 = n-Hex	86%	100	0
b	R_1 = H	R_2 = Ph	80%	33	67

Although useful in the cyclopropyl series, the selenone route is less attractive in the other cases (Scheme 33) due to (i) the concomitant formation of allyl alcohols resulting from the elimination of the intermediary β-hydroxyalkylselenoxide (Scheme 33 compare entry b to a) (ii) the high propensity of β-hydroxyalkylselenones whose carbon bearing the seleno moiety is flanked by one alkyl group to rearrange to ketones (Scheme 33 compare entry b to a). With that respect the rearrangement can be almost completely supp.ressed if the oxidation is carried out in the presence of a base (Scheme 33, entry c). This two steps app.roach to epoxides from ketones does not offer at present advantages over the one implying the direct addition [7] of α-metaloalkylselenone to the same ketone (compare scheme 33 to scheme 8).

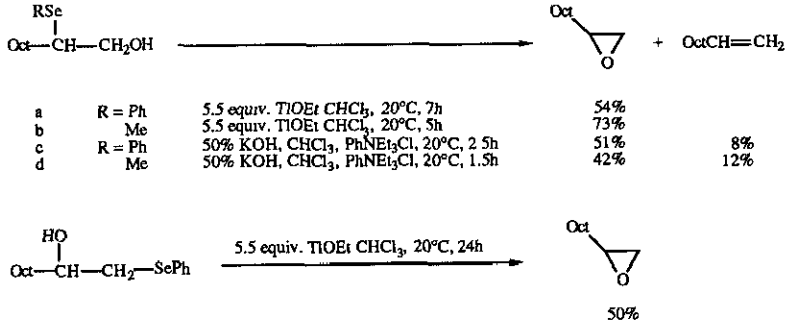
Scheme 33.



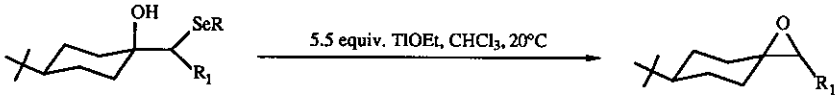
c. Direct synthesis of epoxides involving dihalocarbenes.

We have also found [6a] that β-hydroxyalkylselenides can be directly transformed to the corresponding epoxides on simple reaction, with thallous ethoxide (5.5 equiv.) in chloroform. The reaction proceeds smoothly at room temperature with methylseleno and phenylseleno compounds as well at the condition that the carbon bearing the selenyl moiety is not fully substituted and delivers the epoxide in one step and in reasonably good yield (Schemes 34, 35, 36, see also Scheme 39, entries c and g). This reaction takes place reasonably rapidly (2-4h) with methylseleno derivatives and more slowly with phenylseleno analogues (~ 24h).

Scheme 34.

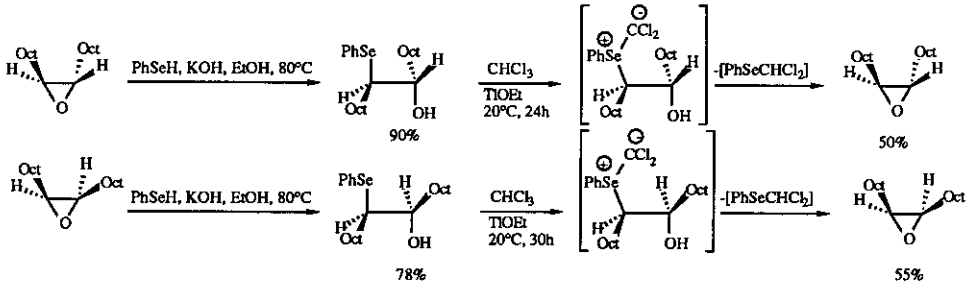


Scheme 35.



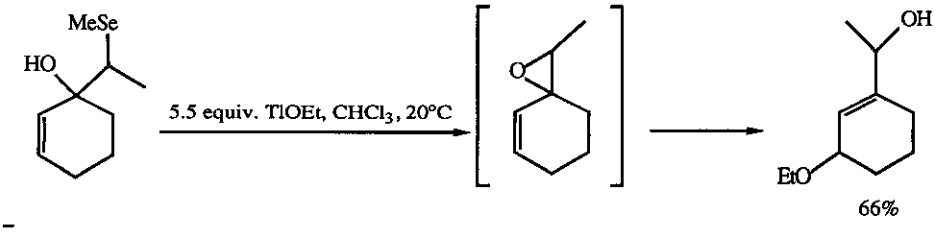
	R	R_1		Yield (time)
a	Ph	H	60% (D)	80% (24h)
b	Ph	Me	78% (E)	80% (24h)
c	Ph	tBu	--	57% (28h)
d	Ph	Ph	--	65% (4h)

Scheme 36.



An epoxide is probably intermediarily produced [19g] from the β-hydroxyalkenylselenide derived from cyclohexenone but under the standard conditions used and further reacts with the excess of thallous ethoxide to deliver the γ-ethoxy-α,β-unsaturated alcohol shown in the scheme 37.

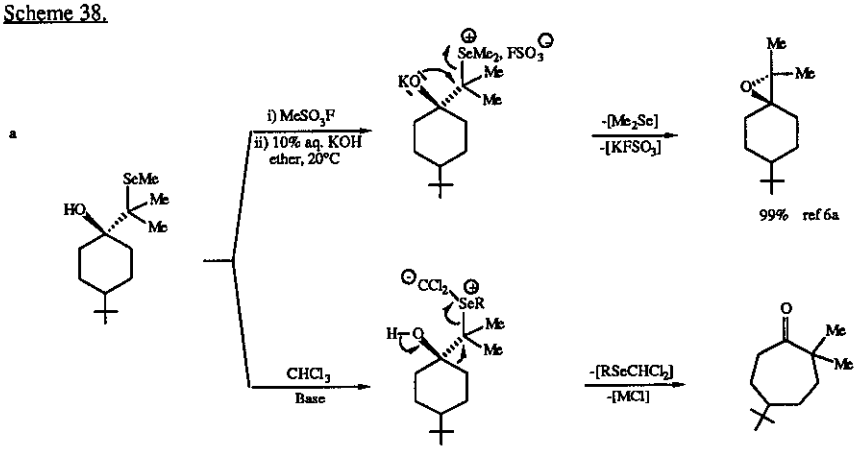
Scheme 37.



β-Hydroxyalkylselenides whose carbon is fully substituted do not lead to epoxides but instead produce rearranged ketones [1j,6b,19] in very high yield(Schemes 38 entry b and 39 entry a). This rearrangement which takes place in both the phenyl- and the methylseleno series of compounds is strictly limited to the above mentioned case and to some compounds in which the hydroxyl group is attached to a four membered cycle even when the other functionalized carbon is monoalkyl substituted (Scheme 39 entry b). This special behavior of cyclobutanol derivatives, probably due to the release of the strain implied in the ring enlargement reaction, is enhanced by the presence of a phenyl group on the migrating carbon atom and proved more effective than the one of related dimethylselenonium salts (Scheme 39 compare entry d to entries e and f). At the contrary, 1-(methylseleno)cyclobutylcarbinols, which do not possess this aptitude to migrate, exclusively lead to

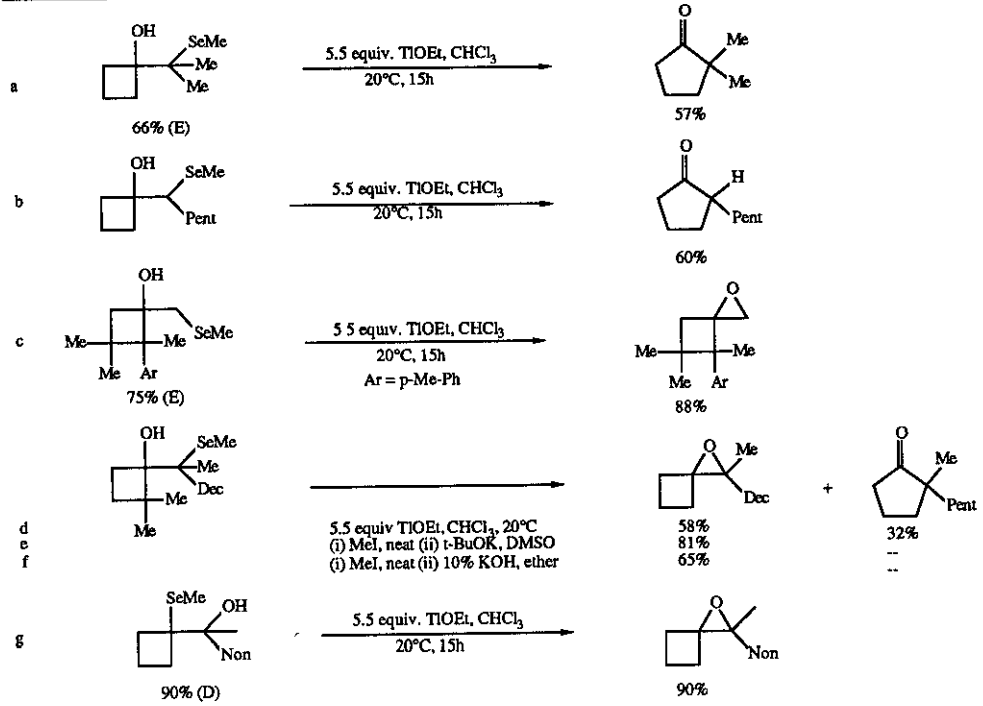
oxaspirohexanes and are the only compounds bearing two alkyl substituents on the carbon bearing the selenyl moiety which do not rearrange under these conditions (Scheme 39, entry g).

Scheme 38.



b $CHCl_3$, TlOEt, 20°C, 8h — R = Ph, Me — 96, 99% ref 19e
c $CHCl_3$, 50% aq KOH, CH_2Cl_2, $PhCH_2NEt_3$, 20°C, 1h — R = Ph, Me — 79, 75% ref 19c

Scheme 39.



Although less general than the related classical two steps method which involves methylseleno compounds discussed previously, this reaction offers definite advantages for phenylseleno derivatives [1b,4a] which otherwise would have required the use of expensive silver tetrafluoroborate.[4a]

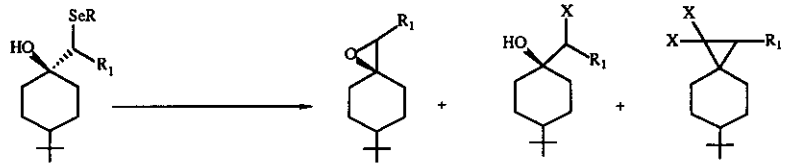
As far as the mechanism is concerned, it was found [6a] that the reaction involves (i) the intermediate formation of a dichlorocarbene by interaction between thallium ethoxide and chloroform, (ii) its selective reaction on the selenyl moiety and (iii) departure of selenodichloromethane with concomitant formation of the epoxide [6a] or the ketone [19b-g] as shown in the schemes 36, 38.

Further support for this mechanism comes from the following observations. (i) Thallous ethoxide in chloroform smoothly allows the synthesis of dichlorocyclopropanes from nucleophilic olefins and dienes [19a]. (ii) The epoxidation reaction does not proceed in methylenedichloride instead of chloroform. (iii) Phenylselenodichloromethane [19g], a quite unstable compound, has been isolated besides the epoxide in those reactions involving β-hydroxyalkylphenylselenides.

Since a dichlorocarbene is involved in this process, it was tempting to perform the reaction under other conditions known to allow the formation of this intermediate as well as of related species. The reaction proved faster when carried out [6a] in methylenedichloride under phase transfer catalysis with 50% aqueous potassium hydroxide solution, chloroform and catalytic amounts of benzyltriethylammonium chloride (method P, Scheme 34, entries c,d and Scheme 40, entries a,b). Although epoxides are usually produced [6a] in quite comparable yields than those obtained with the thallous ethoxide method (method O), the conditions P are less convenient since (i) terminal olefins (Scheme 34, entries c, d) or dichlorocyclopropanes resulting from further reaction of the more reactive olefins are often concomitantly formed (Scheme 40, entry b) and (ii) purification of epoxides from the exogeneous by-products is often quite laborious.

Dibromocarbene, generated from thallous ethoxide in bromoform, also reacts [19g] with β-hydroxyalkylselenides. The reaction is faster but leads instead to bromohydrins (Scheme 40, entry c) and reaction of ethyl diazoacetate (5.6 equiv., neat, 60°C), performed only on the example presented in the Scheme 40 (entry d), produces [19g] selectively the corresponding oxaspiroheptane but in rather modest yield.

Scheme 40.



	R	R1				
a	Me	Me	50% aq. KOH, $CHCl_3$, $PhNEt_3Cl$, 20°C, 3h	60%	-	-
b	Ph	Me	50% aq. KOH, $CHCl_3$, $PhNEt_3Cl$, 20°C, 8h	42%	-	8% (X=Cl)
c	Ph	Me	50% aq. KOH, $CHBr_3$, $PhNEt_3Cl$, 20°C, 3h	-	45% (X=Br)	-
d	Me	H	5.6 equiv. N_2CHCO_2Et, Neat, 60°C	40%	-	-

The stereochemistry of this transformation has been checked[6a] on erythro and threo 9-hydroxy-10-phenylselenooctadecanes. The cyclization was found to proceed with complete inversion of the configuration at the substituted carbon atom (Scheme 36).

C. Conclusion

β-Oxidoalkylselenonium salts and β-oxidoalkylselenones are efficient precursors of epoxides. These compounds are most efficiently prepared by the reaction between carbonyl compounds and organometallics

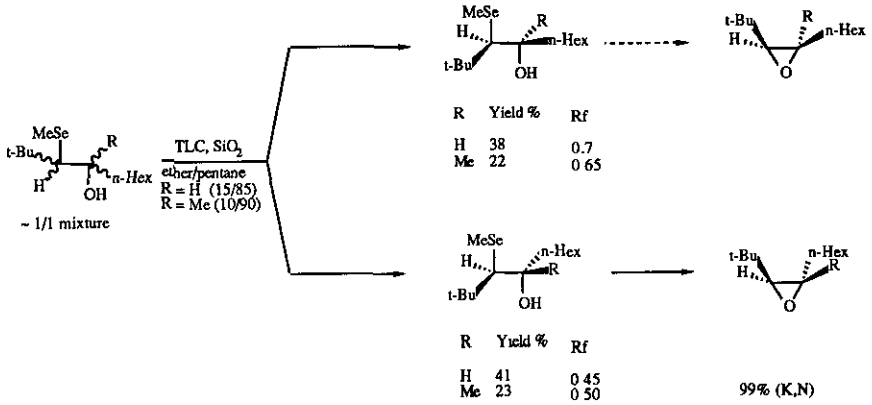
bearing a seleno moiety charged or not. The first route immediately leads to the epoxide whereas the other produces β−hydroxyalkylselenides which require further manipulation to reach the same intermediates.

Although more rapid, the first approach is less general than the second one involving the intermediarily formation of β-hydroxyalkylselenonium salts. The selenonium ylide route is at present limited to those unhindered carbonyl compounds which do not possess enolisable hydrogens whereas the α-lithioalkylselenone is clearly more general, but suffers from severe limitation due to the lack of generality of the methods of synthesis of selenones. However, it offers the clear cut advantage to provide the most straightforward way to oxaspiropentanes especially to those derived from ketones.

The β-hydroxyalkylselenides route proved, apart for the synthesis of the above mentioned oxaspiropentanes, the most general one especially when methylseleno derivatives are involved. It offers the advantage of **(i)** the great availability of α−methylselenoalkyllithiums produced in two steps from aldehydes and ketones under conditions which unambiguously deliver the carbanionic site just at the place where the carbonyl carbon was. **(ii)** the unusually high nucleophilicity of α-methylselenoalkyllithiums toward carbonyl compounds which allow the formation of a new carbon-carbon bond even in the most difficult cases of particularly hindered or enolisable ketones (schemes 17, 18, 19). ***(iii)*** *the easy methylation of the resulting β−hydroxyalkylselenides* (MeI, or Me_2SO_4 neat or $MeSO_3F$ ether) which takes place smoothly even with those derived from the most hindered and enolisable carbonyl compounds and delivers β−hydroxyalkylselenonium salts in almost quantitative yield. **(iv)** the particularly facile purification at that stage of the whole process which latter one allows the obtention of the epoxide without tedious separations. In fact, butylmethylselenide and dimethylselenide concomitantly produced with the β-hydroxyalkylselenide and the epoxide respectively are highly volatile compounds which can be easily pumped out of the medium. Furthermore β−hydroxyalkylselenonium salts on the contrary to other compounds involved as starting materials or by-products in this transformation are insoluble in ether. Therefore, these salts can be freed from any carbonyl compound which could remain from the previous step or from unreacted β−hydroxyalkylselenide, by simply washing it thoroughly with ether. Since the last step takes place almost quantitatively, this process provides the epoxide in analytically pure form after evaporation of the volatile products (Me_2Se, bp_{760} : 58°C and Et_2O).

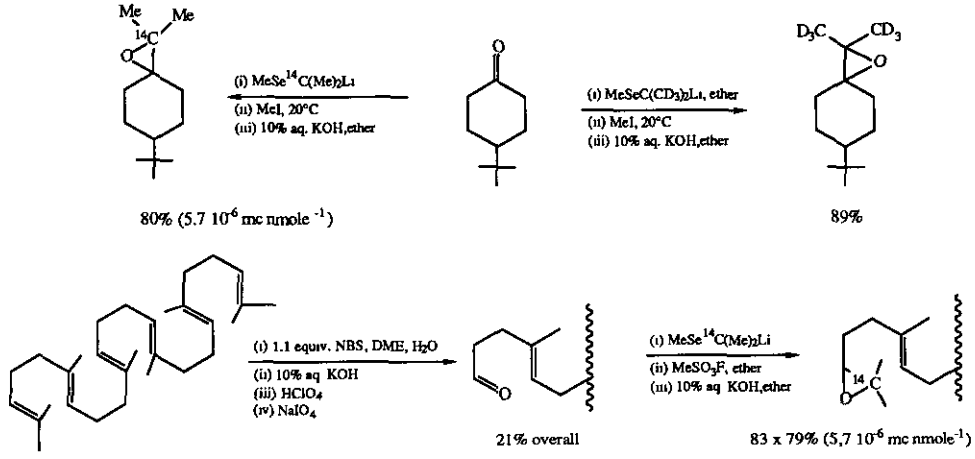
Although the control of the stereochemistry cannot be usually achieved especially with straight chain compounds, the stereoisomeric mixture of β-hydroxyalkylselenides can be often separated into its constituents (Schemes 31 et 41). Since the further steps are completely stereospecific, each of the two stereoisomers of epoxide is thus available.

Scheme 41.



The reaction is relatively of general and allows the synthesis of a large variety of epoxides such as terminal, α,α- and α,β-di-, tri- and tetra-substituted ones [4a,b,d,f-m] as well as of vinyloxiranes [4c,e] from two carbonyl compounds one of them being reductively transformed to an α-methylselenoalkyllithium. Although, each of the two carbonyl compounds can be formally transformed to a selenoalkyllithium, in practice, a judicious selection might be often of some value or even crucial for the success of the transformation. The following rule might help the choice. It is better to transform, to a selenoalkyllithium, the carbonyl compound which is (i) readily available (ii) the least substituted (iii) the least hindered (iv) not aryl or vinyl substituted (v) part of a four membered cycle if the other is a ketone since the resulting β-hydroxyalkylselenide is not as prone to rearrange as the one resulting from the reverse activation (compare for example Scheme 39, entries g to d,e and f).
Finally, acetone is commercially available as fully deuterated derivative as well as radiolabeled with ^{14}C at C_2 or at C_2, C_3. The synthesis of the corresponding selenoacetals has been achieved [4n] and the whole process has even be successfully performed on various substrates (Scheme 42). This has allowed [4n], for example, the straightforward synthesis of 3^{14}C, 2,3-oxidosqualene, a particularly valuable compound for the study of the mechanism of sterols biosynthesis (Scheme 42b).

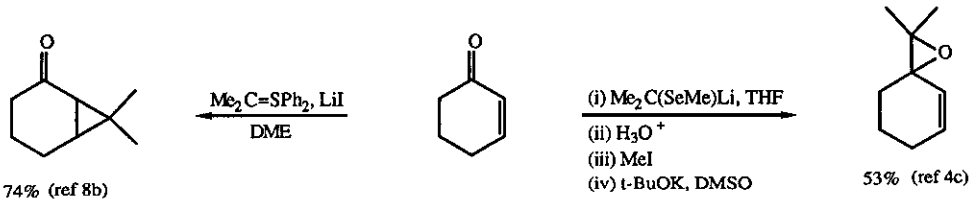
Scheme 42.



The multisteps approach just discussed is related to the one involving α-thioalkyllithiums [11,10,31] or sulfur ylides [8,9].
The thioalkyllithium route [10] is in fact similar to the selenoalkyllithium one and possesses the same advantages but is by far more difficult to achieve due to the tedious preparation of the organometallics [1f]. In fact apart methylthiomethyllithium and α-thiobenzyl- and α-thioallyllithiums which can be obtained [1f,10a] by metalation of the corresponding sulfides, higher homologues are more difficult to prepare [1f,10b,17c,d]. The only general route to such reagents involves mixed S,Se selenoacetals [1f,10b,17c,d] whose synthesis still requires the use of selenols but which is far more difficult than the one of corresponding Se,Se acetals.
The sulfur ylide route is particularly efficient [8,9] and straightforward. It however requires almost the same number of individual reactions as the α-selenoalkyllithium route but these are performed in a different order. Although the sulfur ylide method allows several structural variations, it suffers from (i) the difficult synthesis of almost all sec-alkyldiphenylsulfonium salts which cannot be prepared [8] directly from diphenyl sulfide and

sec-alkyl halides or sec-alcohols due to isomerization of the two latter in the acid medium ($AgBF_4$ or $HClO_4$) needed. These can be however synthesized by a lenghtly procedure which involve the synthesis of a primary alkylsulfonium salt, its metalation and its further alkylation [8,9b] **(ii)** the inertness of sulfur ylides even methylenedimethylsulfurane [10a] towards hindered ketones such as for example 2,2,6,6-tetramethylcyclohexanone **(iii)** the high propensity of sulfur ylides to enolize highly enolisable ketones [9a] such as deoxybenzoin **(iv)** the tendency of those sulfur ylides which bear alkyl substituents on the carbanionic center to add accross the carbon carbon double bond of enones producing [9c] cyclopropyl ketones instead of vinyl oxiranes (Scheme 43) and last but not least **(v)** tedious separations required to remove the diphenyl sulfide from the epoxide at the last stage of the synthesis.

Scheme 43.



74% (ref 8b)

53% (ref 4c)

As already pointed out, all these limitations are avoided if one instead uses the selenium route disclosed above.

REFERENCES

1. (a) D.L. Klayman and W.H.H. Günther, 'Organic Selenium Compounds : their Chemistry and Biology', J. Wiley and sons, New York, 1973. (b) K.B. Sharpless, K.M. Gordon, R.F. Lauer, D.W. Patrick, S.P. Singer, and M.W. Young, Chem. Scripta, 1975, 8A, 9. (c) D.L.J. Clive, Tetrahedron, 1978, 34, 1049. (d) H.J. Reich, 'Oxidation in Organic Chemistry', Part C, ed. by W.S. Trahanovsky, Academic Press, New York, Vol. 5C, 1978.(e) H.J. Reich, Acc. Chem. Res., 1979, 12, 22. (f) A. Krief, Tetrahedron, 1980, 36, 2531. (g) K.C. Nicolaou and N.A. Petasis, "Selenium in Natural Products Synthesis", CIS Inc., Philadelphia, 1984. (h) D. Liotta, Acc. Chem. Res., 1984, 17,28. (i) C. Paulmier, 'Selenium Reagents and Intermediates in Organic Synthesis', ed. by J.E. Baldwin, Pergamon Press, Oxford, 1986. (j) S. Patai and Z. Rappoport, 'The Chemistry of Selenium and Tellurium Compounds', Vol. 1 and 2, J. Wiley, Chichester, 1986 and 1987. (k) D. Liotta, 'Organoselenium Chemistry', J. Wiley and sons, Chichester, 1987. (l) A. Krief, 'Topics in Current Chemistry', Springer-Verlag, Berlin, 1987, 135, 1. (m) A. Krief and L. Hevesi, 'Organoselenium Chemistry I, Functionnal Group Transformation', Springer-Verlag, Berlin, 1988.
2. (a) For a review article of this specific reaction, see our reference 1m, chapter 8, pp.. 106-118 (b) T. Kametani, H. Nemoto, and H. Fukumoto, Heterocycles, 1977, 6, 1365. (c) P.A. Grieco, Y. Yokoyama, S. Gilman, and M. Nishizawa, J. Org. Chem., 1977, 42, 2034. (d) T. Hori and K.B. Sharpless, J. Org. Chem., 1978, 43, 1689. (e) H.J. Reich, F. Chow , and S.L. Peake, Synthesis, 1978, 299. (f) R.T. Taylor and L.A. Flood, J. Org. Chem., 1983, 48, 5160.
3. (a) W. Dumont, P. Bayet , and A. Krief, Angew. Chem., Int. Ed. Eng., 1974, 13, 274. (b) K. Takaki, M. Yasumura , and K. Negoro, Angew. Chem., Int. Ed. Eng., 1981, 20, 672. This report proved incorrect since we have been unable to reproduce several of the reported results see reference 166 in our reference 2b.
4. (a) W. Dumont and A. Krief, Angew. Chem., Int. Ed. Eng., 1975, 14, 350. (b) D. Van Ende, W. Dumont , and A. Krief, Angew. Chem., Int. Ed. Eng., 1975, 14, 700. (c) D. Van Ende and A. Krief,

Tetrahedron Lett., 1976, 457. (d) D. Labar, A. Krief , and L. Hevesi, Tetrahedron Lett., 1978, 3967. (e) S. Spreutels, Memoire de Licence, Facultés N-D. de la Paix, Namur, June 1979. (f) S. Halazy and A. Krief, Tetrahedron Lett., 1980, 21, 1997. (g) D. Labar and A. Krief, J. Chem. Soc., Chem. Commun., 1982, 564. (h) S. Halazy and A. Krief, J. Chem. Soc., Chem. Commun., 1979, 1136. (i) J.-R. Schauder and A. Krief, Tetrahedron Lett., 1982, 23, 4389. (j) J.-R. Schauder, PHD Thesis, Namur, 1985. (k) D. Labar, A. Krief, B. Norberg, G. Evrard , and F. Durant, Bull. Soc. Chim. Belg. 1985, 94, 1083. (l) D. Labar, PHD Thesis, Facultés N-D. de le Paix, Namur, 1985. (m) D. Labar, unpublished results from our laboratory. (n) A. Krief, W. Dumont, D. Van Ende, D. Labar, J.-R. Schauder, J.-L. Laboureur , and G. Chaboteaux, Proceeding of the Third International Conference on Chemistry and Biotechnology. Sofia, Bulgary, July 1985.

5. (a) A.-M. Leonard-Coppens and A. Krief, Tetrahedron Lett., 1976, 3227. (b) J.-N. Denis, J. Vicens , and A. Krief, Tetrahedron Lett., 1979, 2697.
6. (a) J.-L. Laboureur, W. Dumont , and A. Krief, Tetrahedron Lett., 1984, 25, 4569. (b) S. Halazy, F. Zutterman , and A. Krief, Tetrahedron Lett., 1982, 23, 4385.
7. (a) A. Krief, W. Dumont , and J.-N. Denis, J. Chem. Soc., Chem. Commun., 1985, 571. (b) A. Krief, W. Dumont , and J.-L. Laboureur, Tetrahedron Lett., 1988, 29, 3265. (c) T.Q. Lê, Memoire de Licence, Facultés N-D. de la Paix, Namur, June 1988. (d) S. Uemura, K. Ohe , and N. Sugita, J. Chem. Soc., Chem. Commun., 1988, 111.
8. (a) B.M. Trost and L.S. Melvin, 'Sulfur Ylides', Academic Press, New York, 1975. (b) E. Block, 'Reaction of Organosulfur Compounds', Academic Press, New York, 1978, Chapter 3, pp. 91-127.
9. (a) E.J. Corey and M. Chaykovsky, J. Am. Chem. Soc., 1965, 87, 1353. (b) E. J. Corey, M. Jautelat , and W. Opp.olzer, Tetrahedron Lett., 1967, 2325. (c) E.J. Corey and M. Jautelat, J. Am. Chem. Soc., 1967, 89, 3912.
10. (a) J. R. Shanklin, C.R. Johnson, J. Ollinger , and R.M. Coates, J. Am. Chem. Soc., 1973, 95, 3429. (b) A. Anciaux, A. Eman, W. Dumont , and A. Krief, Tetrahedron Lett., 1975, 1617.
11. (a) W. Dumont, P. Bayet , and A. Krief, Angew. Chem., Int. Ed. Eng., 1974, 13, 804.(b) D. Labar, W. Dumont, L. Hevesi , and A. Krief, Tetrahedron Lett., 1978, 1145.
12. (a) A. Krief, W. Dumont, J.-N. Denis, G. Evrard , and B. Norberg, J. Chem. Soc., Chem. Commun., 1985, 569. (b) A. Krief, W. Dumont , and A.-F. De Mahieu, Tetrahedron Lett., 1988, 29, 3269.
13. B.M. Trost and M.J. Bogdanowicz, J. Am. Chem. Soc., 1973, 95, 5298, 5311 and 5321.
14. (a) M. Braun, R. Dammann , and D. Seebach, Chem. Ber., 1975, 108, 2368. (b) T. Hiyama, S. Takehara, K. Kitatani , and H. Nozaki, Tetrahedron Lett. , 1974, 3295.
15. (a) W. Jenny, Helv. Chim. Acta, 1953, 36, 1279. (b) K.B. Sharpless and R.F. Lauer, J. Org. Chem., 1974, 39, 429. (c) D.L.J. Clive, J. Chem. Soc., Chem. Commun., 1974, 100.
16. (a) H.J. Reich, S. Wollowitz, J.E. Trend, F. Chow , and D.F. Wendelborn, J. Org. Chem., 1978, 43, 1697. (b) D. Labar and A. Krief, Bull. Soc. Chim. Belg., 1984, 93, 1005. (c) H.J. Reich, W.W. Willis , and S. Wollowitz, Tetrahedron Lett., 1982, 23, 3319. (d) J.L. Kice, F. Mc Afee , and H. Slebocka-Tilk, Tetrahedron Lett., 1982, 23, 3323.
17. (a) D. Seebach and N. Peleties, Angew. Chem., Int. Ed. Eng., 1969, 8, 450. (b) D. Seebach and N. Peleties, Chem. Ber., 1972, 105, 511. (c) D. Seebach and A.K. Beck, Angew. Chem., Int. Ed. Eng., 1974, 13, 806. (d) D. Seebach, N. Meyer , and A.K. Beck, Liebigs Ann., 1977, 846.
18. (a) J. Remion, W. Dumont , and A. Krief, Tetrahedron Lett., 1976, 1385. (b) J. Remion and A. Krief, Tetrahedron Lett., 1976, 3743. (c) S. Halazy, J. Lucchetti , and A. Krief, Tetrahedron Lett., 1978, 3971. (d) S. Halazy and A. Krief, Tetrahedron Lett., 1980, 21, 1997. (e) A. Krief, W. Dumont, M. Clarembeau, G. Bernard , and E. Badaoui, Tetrahedron, in print. (f) A. Krief, W. Dumont, M.

Clarembeau , and E. Badaoui, Tetrahedron, in print. (g) S. Halazy and A. Krief, J. Chem. Soc., Chem. Commun., 1982, 1200. (h) S. Halazy, unpublished results from our laboratory.

19. (a) D. Labar, J.-L. Laboureur , and A. Krief, Tetrahedron Lett., 1982, 23, 983. (b) J.-L. Laboureur and A. Krief, Tetrahedron Lett., 1984, 25, 2713. (c) A. Krief and J.-L. Laboureur, J. Chem. Soc., Chem. Commun., 1986, 702. (d) A. Krief and J.-L. Laboureur, Tetrahedron Lett., 1987, 28, 1545. (e) A. Krief, J.-L. Laboureur , and W. Dumont, Tetrahedron Lett., 1987, 28, 1549. (f) L.A. Paquette, J.R. Peterson, and R.J. Ross, J. Org. Chem.,1985, 50, 5200. (g) J.-L. Laboureur, unpublished results from our laboratory.
20. (a) O. House, 'Modern Synthetic Reactions', 2nd Ed., W.A. Benjamin, New York, 1972. (b) J. March, 'Advanced Organic Chemistry', 3rd Ed.,J. Wiley and sons, New York, 1985. (c) G. Dittus, 'Methoden der Organischen Chemie', Houben-Weyl, Bd VI/3, 1965, 367. (d) D. Swern, 'Organic Reactions', Vol. VII, 1953, 378.
21. (a) K.B. Sharpless, R.F. Lauer , and A.Y. Teranishi, J. Am. Chem. Soc., 1976, 95, 6137. (b) J.-N. Denis, W. Dumont , and A. Krief, Tetrahedron Lett., 1976, 453. (c) J. Lucchetti and A. Krief, C. R. Acad. Sci. Paris, Ser. C, 1979, 288, 537. (d) R. Baudat and M. Petrizilka, Helv. Chim. Acta, 1979, 62, 1406. (e) G.H. Posner and M.J. Chapdelaine, Tetrahedron Lett. , 1977, 3227. (f) D.H.R. Barton, D.J. Lester, W.B. Motherwell , and M.T. Barros Papoula, J. Chem. Soc., Chem. Commun., 1980, 246.
22. M. Cherest, H. Felkin , and N. Prudent, Tetrahedron Lett., 1968, 2199 and references cited.
23. J.N. Cornforth, R.H. Cornforth , and K.K. Mathew, J. Chem. Soc., 1959, 112.
24. (a) H.J. Reich and S.K. Shah, J. Am. Chem. Soc., 1975, 97, 3250. (b) H.J. Reich and F. Chow, J. Chem. Soc., Chem. Commun., 1975, 790. (c) R.C. Gadwood, J. Org. Chem., 1983, 48, 2098. (d) R.C. Gadwood, I.M. Mallick , and A.J. De Winter, J. Org. Chem.,1987, 52, 774.
25. (a) H.J. Reich, F. Chow , and S.K. Shah, J. Am. Chem. Soc., 1979, 101, 6638. (b) R.H. Mitchell, J. Chem. Soc., Chem. Commun., 1974, 990. (c) M. Clarembeau and A. Krief, Tetrahedron Lett., 1986, 27, 1723, ibid., 1986, 27, 4917.
26. (a) H.J. Reich, J. Org. Chem., 1975, 40, 2570. (b) M.R. Binns, R.K. Haynes, T.L. Houston , and W.R. Jakson, Tetrahedron Lett., 1980, 573. (c) H.J. Reich, M.C. Clark , and W.W. Willis, J. Org. Chem., 1982, 47, 1618. (d) M. Clarembeau and A. Krief, Tetrahedron Lett., 1984, 25, 3629. (e) L. Hevesi, K.M. Nsunda , and M. Renard, Bull. Soc. Chim. Belg., 1985, 94, 1039. (f) H.J. Reich and S.K. Shah, J. Am. Chem. Soc., 1977, 99, 263.
27. (a) M. Clarembeau, A. Cravador, W. Dumont, L. Hevesi, A. Krief, J. Lucchetti , and D. Van Ende, Tetrahedron, 1985, 41, 4793, and references cited. (b) A. Cravador and A. Krief, C. R. Acad. Sci. Paris, Ser. C, 1979, 267.
28. (a) L. Fitjer, H. Scheuermann , and D. Wehle, Tetrahedron Lett., 1984, 25, 2329. (b) Kindly provided by Prof. D.H.R. Barton, Institut des Substances Naturelles, Gif-sur-Yvette, France.
29. K.B. Sharpless and R.F. Lauer, J. Am. Chem. Soc., 1973, 95, 2697.
30. C.R. Johnson, C.W. Schroek , and J.M. Shanklin, J. Am. Chem. Soc., 1973, 95, 7424.
31. W. Dumont and A. Krief, J. Chem. Soc., Chem. Commun., 1980, 673.

Received, 19th September, 1988