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NEW REGIOSPECIFIC ROUTE TO β - γ UNSATURATED ALCOHOLS AND β - γ UNSATURATED KETONES NEW METHODOLOGY FOR α - β UNSATURATED KETONES SYNTHESIS

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We report here on new methods which allow the regiospecific synthesis of $\beta\gamma$ unsaturated alcohols (homoallyl alcohols) and the corresponding $\beta\gamma$ unsaturated ketones as well as $\alpha\beta$ unsaturated ketone from the same precursor and by generating a new C-C bond.

These transformations take advantage of the clean reaction of α -selenoalkyllithium 2^{1} (easily prepared from carbonyl compounds) with epoxides 3^{2} (THF, -78°C, 2hrs/ 25°C, 1hr) which produces γ -hydroxyselenides 4^{3} in 66 to 84% yield (Scheme I).

SCHEME I



	R	R ₁	R ₂	R ₃ In	eld 4 %
a b c d e f g h	CH ₃ CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3 CH3	$ \begin{array}{c} H \\ CH_{3}^{-}(CH_{2})_{8} \\ CH_{3}^{-}(CH_{2})_{4} \\ C_{6}H_{5}^{-}CH_{2} \\ CH_{2}^{-}(CH_{2})_{2} \\ H \\ CH_{3}^{-}(CH_{2})_{8} \\ CH_{3}^{-}(CH_{2})_{4} \end{array} $	н н н - Сн ₂ н н	$\begin{array}{c} {}^{\rm CH}_{\rm 3} \\ {}^{\rm CH}_{\rm 3} \\ {}^{\rm CH}_{\rm 3} \\ {}^{\rm CH}_{\rm 13} \\ {}^{\rm CH}_{\rm 3} \\ {}^{\rm CH}_{\rm 13} \\ {}^{\rm C}_{\rm 6}{}^{\rm H}_{\rm 13} \\ {}^{\rm H} \\ {}^{\rm C}_{\rm 6}{}^{\rm H}_{\rm 13} \end{array}$	66 71 80 75 80 83 81 84

From the spectroscopical data it is clear that α -selenocarbanions react specifically, as expected, on the least substituted carbon of the epoxides. These results are ascertained by the comparison of spectra of the γ -hydroxyselenides (<u>4a</u>, Scheme I) with the one (<u>4a</u>) prepared unambiguous ly according to the following scheme:

Selenols are added to the C-C double bond of unsaturated carbonyl compounds 5 (ether, catalytic amount piperidine, 25°C, 8-16 hrs) producing the β -selenocarbonyl derivatives 6 in high yield. Reaction of 6 with a Grignard reagent produces the desired γ -hydroxyselenides 4.



The second part of this paper deals with the selective activation of the selenyl moiety of the γ -hydroxyselenides¹³. Thus γ -hydroxyselenides are transformed in high yield to the corresponding selenonium salts $\underline{7}^5$ (CH₃I: 2 eq., neat, 20°C, 5hrs) which are specifically transformed to homoallyl alcohols in high yield when treated with potassium t.butylate (tbuOK, leq./DMSO, 20°C, 4hrs, MethodA)⁶ or under phase transfert reaction conditions (KOH 50% in water, CH₂Cl₂, Adogen 464, Method B)⁶.



	R l	R ₂	R ₃	yield in <u>7</u> %	yield in <u>9</u> %
a b c d e	${}^{\rm H}_{{\rm nC_9H_19}} \\ {\rm nC_5H_{11}}_{{\rm C_6H_5-CH_2}} \\ {\rm CH_2^-({\rm CH_2})} \\$	н н н 4-сн ₂	$CH_{3} CH_{3} CH_{3} CH_{3} CH_{3} CH_{13} CH_{13} CH_{3} CH_{3$	86 87 86 70 70	- 75(A) 86(A) 91(A)-73(B) 65(A)

The high specificity of this transformation can be explained by the cyclic elimination presented in the Scheme III, and is remarquable 7 if one knowsthe different decomposition pathways describes for γ -heterosubstituted alcoholates.

One can also readily produce a C-C double bond from compounds $\underline{4}$ by using the well known propensity of selenoxides to decompose into alcenes; but reaction is not generally regiospecific 2^{b} . Thus when 1-pheny1-3-(selenomethy1)-undecane-5-ol $\underline{4d}$ is subjected to the oxidation reaction(H₂O₂ excess/THF;0°C,30 min.,25°C,1hr) a mixture of the homoally1 alcohol $\underline{9d}$ and the corresponding ally1-alcohol $\underline{10d}$ is as expected produced (83% overall yield - $\underline{9d}/\underline{10d}$: 1/1).

γ-hydroxyselenides have also been found powerful precursor of αβ unsaturated carbonyl compounds. The main problem is to oxidize the alcohol prior the elimination of the selenyl moiety takes place, in order to direct the elimination specifically with the hydrogen α to the carbonyl (which becomes much more acidic). We have found that is the case when γ -hydroxyselenide is reacted with Jones' reagent $(CrO_3/H_2SO_4$ 3 eq., Acetone, 0°C, 3hrs; 25°C, 24hrs)⁸ conditions which are known to be effective for the oxidation of both alcohol and selenyl functions.



This is also the case when γ -hydroxyselenonium salt <u>7d</u> is treated with the same reagent (CrO₃/H₂SO₄/acetone,25°C,16 hrs)

$$\begin{bmatrix} \mathbf{I}^{-} (CH_3)_2 - Se^{+} & C_6H_{13} \\ C_6H_5 - (CH_2)_2 - CH - CH_2 - CH \\ \mathbf{I} \\ \mathbf{OH} \end{bmatrix} \begin{bmatrix} \mathbf{I}^{-} (CH_3)_2 - Se^{+} \\ C_6H_5 - (CH_2)_2 - CH - CH_2 - C - C_6H_{13} \\ \mathbf{OH} \end{bmatrix} \longrightarrow \begin{bmatrix} C_6H_5 - (CH_2)_2 - CH - CH_2 -$$

We have controled that no isomerisation of the double bond (to the more conjugated one) takes place, under these conditions. Thus the homoallyl alcohol, 1-pheny1-2-undecene-5-ol is regiospecifically transformed to the corresponding By unsaturated ketone in 70% overall yield.

The transformation described in this report may be of special interest for synthetic chemist. For instance, the synthesis of homoallyl alcohol $\underline{9}$ by combination of Schemes II, and III proposes a new regiospecific reductive isomerisation of $\alpha\beta$ unsaturated carbonyl compounds to the $\beta\gamma$ unsaturated alcohols and in the synthesis of the same alcohol $\underline{9}$ by the combination of Schemes I and III, the selenocarbanion acts as a masked vinyl anion.

Finally the last transformation give the results of an aldol condensation or a Wittig reaction with inverse activation compared both to the classical or modified <u>aldol condensation</u> or to <u>negative</u> acyl methodology (see the following scheme).

Our method over and above the methodology problem has the advantage of high selectivity in C-C bond formation (which is sometimes the lack of the aldol reactions) and is unaware of the problems sometimes uncountered in both other route for C-C double bond formation (by deshydratation of the β -hydroxycarbonyl compounds). However, one need further examples to prove the generality for our proposed method and optimization of the results of the last step. We are currently working in this area



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- 3. Synthesis of γ -hydroxyselenides 4 : nBuLi (5.10⁻³m) (2N in hexane, Merck) is slowly added at -78°C under argon to a solution of selenoacetal $(5.10^{-3}m)$ in anhydrous THF (10 ml). After lhrat $(-78^{\circ}C)$ the epoxide (5.10^{-3} m) in THF (5 ml) is added and the resulting solution is stirred for 2 hrs at -78°C and 1 hr at 25°C, hydrolyzed, extracted and dried. The γ -hydroxyselenide is purified by preparative thick layer chromatography (PLC (SiO2, Merck, 2 mm, ether/pentane 1:9, Rf : 2.5). The two diasteroisomers are obtained as a 1:1 mixture.
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- 5. Synthesis of γ-hydroxyselenonium salt 7 : γ-hydroxyselenide 4 (2.10⁻³m) is stirred with methyl-iodide (4 10⁻³m) for 4 hrs at 20°C. The mixture (which becomes rapidly crystalline) is washed three times with anhydrous ether in order to remove the eventually unreacted selenide 4 and the resulting salt is used without further purification.
- 6. Synthesis of homoallylic alcohol: (the stereochemical aspect of this reaction is under investigation Method A : The selenonium salt $7(10^{-3}m)$ in DMSO (distilled from CaH₂, 5 ml) is added at $20^{\circ}C$ under argon to a solution of potassium tertiobutoxyde : (Merck, sublimated 10^{-3} m) in DMSO(5 ml). The mixture is stirred 4 hrs at 25°C, hydrolyzed, extracted and dried. The homoallyl alcohol*is purified by PLC (SiO2, Merck, 2 mm, ether/pentane 2/8, Rf=0.31) * sometimes, the crude product is contamined by a little amount of Y-hydroxyselenide. It was removed as a selenonium salt 7 by stirring the crude mixture with methyl iodide before extrac-

tion with ether. Method B : Potassium hydroxyde 50% (10 ml, H_2 0) is added to a mixture of the selenonium salt $(0.5 \ 10^{-3}\text{m})$ and 0.050g of adogen 464 (Merck) in methylene chloride (15ml). The mixture is stir-

red for 5hrs. Usual work up produces the homoallyl alcohol. Olefin arising from C-C bond fragmentation is obtained in 10% yield in both method A and B. 7. W. Fisher and A. Grob, Tet. Lett., 3547 (1975) and references cited herein

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