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C_5-Branched Vinyltin Acetals as Versatile Tools for Terpenic Synthesis

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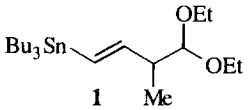
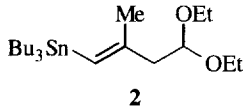
Abstract : C_5-branched vinyltin acetals **1** and **2** obtained by stannylmetallation of homopropargyl acetals with $Bu_3SnMgMe$ in the presence of cuprous cyanide have been proved to be efficient storable precursors for the synthesis of terpenoids.

Due to the importance of terpenoids[1], it is of interest to propose building blocks having large potentialities for their synthesis. Considering the backbone of this class of compounds, vinylic branched C_5-units, having both a nucleophilic site and an electrophilic site, appear of high interest and vinyltin acetals **1** and **2** can be expected to be appropriate stable precursors.

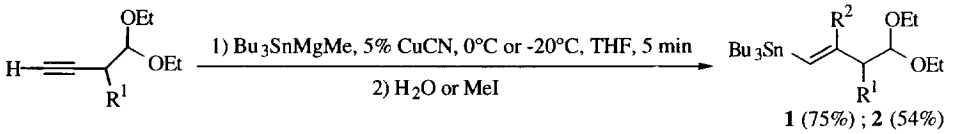


1



2

Unfortunately, the free radical hydrostannation of 3-(diethoxymethyl)-but-1-yne is non-stereospecific (thermodynamic mixture of geometrical isomers : E/Z = 87/13 is obtained)[2] and in consequence, we choose the stannylmetallation routes to obtain **1** and **2**. However, while stannylmetallations of alkynes occur generally in a *syn* fashion, the regioselectivity of the addition is highly dependent on the stannylmetallation reagent, on the substrate and on the experimental conditions[3-8]. For instance, using the Lipshutz reagent[4], the stannylcupration of propargyl acetals occurs cleanly at the β-position[5,6] while stannylcupration of homopropargyl acetals affords mixture of regioisomers[5]. Until now, in the latter case, we have been unable to drive the reaction of Lipshutz reagent to the desired regioisomer adding, for instance, HMPA in THF in order to shift the reaction to the thermodynamic vinylcopper intermediate, as recently described by Oehlschlager for the stannylcupration of 1-alkoxyalkynes[7].The desired vinyltins **1** (R^1=Me, R^2=H) and **2** (R^1=H, R^2=Me) were obtained using tributylstannylmethylmagnesium in the presence of cuprous cyanide (5%) according to Nozaki[8] for the stannylmetallation of the homopropargylic acetals. The advantage of this method, in this case, is the good regioselectivity associated with a higher reactivity of the vinylmagnesium intermediate in alkylation reactions.

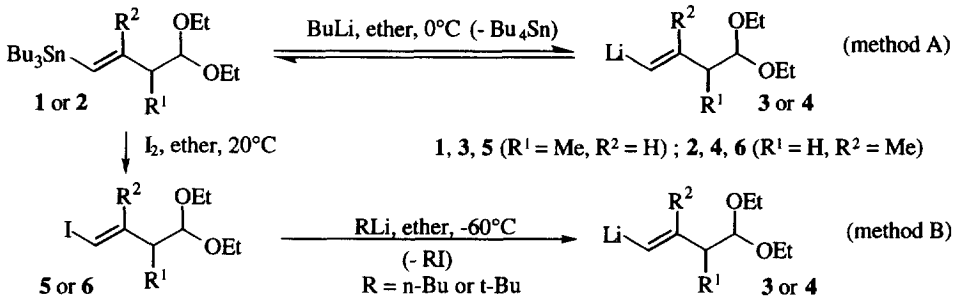


1 (75%) ; **2** (54%)

In the case of the synthesis of **2**, compared to our previous report[5], the preparation has been improved in terms of purity since the amount of protonated derivative ($R^1 = R^2 = H$) has been maintained under 2 %[9].
In such conditions, vinyltin acetals **1** and **2** appear to be reasonably accessible precursors whose potential must be evaluated in organic synthesis both as precursors of vinyllithium reagents[11] and in cross coupling reactions[12].

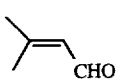
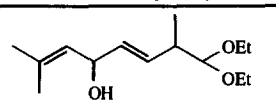
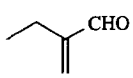
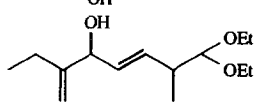
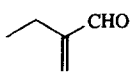
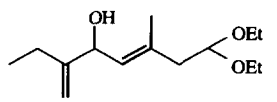
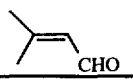
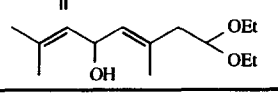
Use of 1 and 2 as precursors of vinyllithium reagents :

When transmetallation reaction of **1** or **2** with butyllithium was attempted in ether at 0°C (method A), the yields in vinyllithium reagents **3** or **4** were limited by the transmetallation equilibrium (cf table I). To circumvent this problem (method B), these vinyltins were first converted into vinyl iodides (I_2, ether, 20°C, 1h) before performing the halogen-metal exchange (n-BuLi or t-BuLi, ether, -60°C, 1h). According to this last route the vinyllithium reagents **3** or **4** were obtained in good yields :



To exemplify the possibilities brought by this type of reagent, they have been reacted with senecialdehyde and 2-ethylacrolein to give monoterpenoids skeletons.

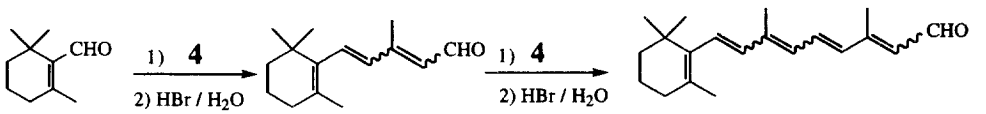
Table I : Reactivity of Vinyllithiums **3** and **4** with Senecialdehyde and 2-Ethylacrolein.

Entry	Vinyltin	Vinyllithium	Aldehyde	Adduct (after hydrolysis)	N°	Yield[(a)]
1	**1**	**3** (method A)			**7**[(b)]	45%
2	**1**	**3** (method B)			**7**[(b)]	71%
3	**1**	**3** (method A)			**8**	62%
4	**1**	**3** (method B)			**8**	76%
5	**2**	**4** (method A)			**9**	27%
6	**2**	**4** (method B)			**9**	74%
7	**2**	**4** (method B)			**10**	93%

[(a)] Isolated yields from vinyltin acetals **1** and **2** using stoechiometrical amounts of reagents. Physicochemical data are in agreement with the above mentioned structures. [(b)] **7** isomerized into the conjugated dienic tertiary allylic alcohol in the presence of traces of acids.

The results summarized in table I underline the remarkable versatility of these reagents to reach usual or unusual monoterpenoids, as it is possible to obtain head-to-head, head-to-tail, tail-to-head or tail-to-tail monoterpenic skeletons.

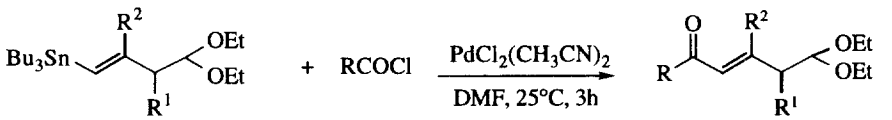
In connexion with this work, we have been also able to obtain retinal from β-cyclocitral using vinyllithium **4** (obtained according to method B) in an iterative fashion : the initial hydroxyacetal was hydrolysed into β-ionylidene acetaldehyde which was subsequently reacted with **4** to give retinal after hydrolysis (47 % unoptimized yield from β-cyclocitral)[13].



From these initial results, it appears that vinyllithiums **3** and **4** can complement efficiently other recent organometallic approaches to terpenoids[14-17].

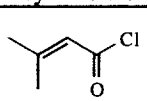
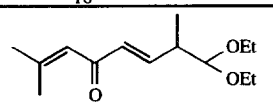
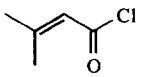
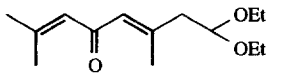
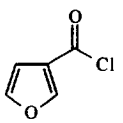
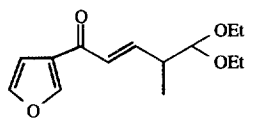
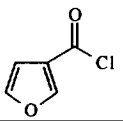
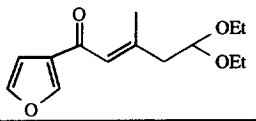
*Use of **1** and **2** in cross coupling reactions :*

In order to examine the possibility to reach branched C_{10}-oxoacetals, we have examined the cross coupling of vinyltin acetals with senecioyl chloride and 3-furoyl chloride. As expected in this case, the reaction of acyl chloride at the acetal function does not interfer and the desired compounds were obtained in about 60 % isolated yields (cf table II), according to :



1 or **2** **11-14**

Table II : Cross Coupling of Vinyltin Acetals **1** and **2** with Senecioyl Chloride and 3-Furoyl Chloride.

Entry	Vinyltin	Acyl chloride	C_{10}-ketoacetals	N°	Yield[(a)]
1	**1**			**11**	56%
2	**2**			**12**	59%
3	**1**			**13**	64%
4	**2**			**14**	58%

(a) Isolated yields in pure compounds having physicochemical data in agreement with the above mentioned structures.

Here again, appropriate combination of vinyltins and acyl chlorides allows access to terpenoids having head-to-head, head-to-tail, tail-to-head or tail-to-tail backbones. The above results demonstrate the great versatility of vinyltin acetals **1** and **2** for terpenic synthesis and we are presently developing applications using these new building blocks and the obtained functional terpenoid products.

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9. *Typical procedure for the preparation of 2 :* $Bu_3SnMgMe$ was obtained at -20°C by addition of MeMgI (78 mmol, 3.2 M in ether) to Bu_3SnLi (78 mmol, in 40 ml THF) previously prepared by deprotonation of Bu_3SnH with iPr_2NLi. At -20°C, the $Bu_3SnMgMe$ solution was subsequently stirred with CuCN (5% mol) before dropwise addition of alkyne (0.4 eq) and quenching with methyl iodide (2.3 eq). After usual workup, vinyltin **2** was isolated by distillation (Eb $_{0.06}$ = 114°C).
The E-configuration for compound **2** has been unambiguously assigned on the basis of $^3J_{Sn-^{13}C}$ observed for the allylic carbon atoms : CH_3 (δ = 25.1 ppm, $^3J_{Sn-C}$ = 35.4 Hz) and CH_2 (δ = 46 ppm, $^3J_{Sn-C}$ = 58.6 Hz), the *cis* coupling being lower than the *trans* coupling[10].
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