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Polar Allyl Type Organometallics as Key Intermediates in Regio- and Stereocontrolled Reactions : Conformational Mobilities and Preferences

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1. INTRODUCTION

Polar organometallic reagents are among the preferred tools of modern synthesis [1]. What makes them so appealing is a combination of valuable properties : *versatility*, *reactivity* and *selectivity*. Selectivity means preference for a given reaction channel if there is a choice among several related ones. Very crudely, we may distinguish between competing reaction types (*typoselectivity* or *chemoselectivity*), reaction sites (*regioselectivity* or *positional selectivity*) and topomorphologies (*stereoselectivity*). This article focuses on special stereochemical features associated with resonance stabilized organometallic intermediates of the allyl type : their conformational mobility and their conformational preferences. Although these two issues are interconnected, we shall differentiate carefully between them. In one case we deal with a kinetic, in the other with a thermodynamic phenomenon. When an *equilibrium* is established between two (or several) geometrical isomers, we compare the structural quality of ground state species. What can be learned is to which extent the spatial array affects the attractive and repulsive forces that determine the thermodynamic stability of a chemical entity. If one conformer is energetically less favorable than another, it can still persist. A spontaneous transformation will only occur if an "inexpensive" mechanism is available to mediate the stereomutation. The process will be the faster the lower the barrier of activation. In other words, internal mobility has to do with *rates*. These rates reflect the differences in free enthalpies of ground state and transition state structures. This type of comparison is particularly rewarding in the case of allylic organometallics, since the ground state structures are extensively delocalized while at the transition state the resonance is partially or completely turned off. Thus we gain insight into the electronic properties of the species under inspection.

All this sounds quite abstract, if not esoteric. However, as we shall recognize later, the conformational behavior of allyl type organometallics is of eminent practical significance. Indeed, it offers an extremely simple and yet powerful instrument to achieve stereocontrol over an entire area of addition and substitution, including carbon-carbon linking, reactions.

2. THE STRUCTURAL FLEXIBILITY OF ORGANOMETALLIC SPECIES

There are two major modes of stereomutation which are accessible to organometallic compounds but not to their hydrocarbon precursors from which they are derived by deprotonation : the *pyramidal inversion* of metal-bearing carbon centers and the *torsional isomerization* of allyl moieties. The principal characteristics of these processes become more evident if we first recall the well-established analogies in the amine series. Amines are isoelectronically related to carbanions, the imaginary torsos of organometallic species from which the inorganic counterparts have been stripped off.

2.1 The Configurational Inversion of Pyramidal Structures

The tetragonal configuration of an ammonium salt is permanent. If the positively charged nitrogen center carries one hydrogen and three other different substituents, it is at least, in principle, possible to separate a mixture containing equal amounts of the two antipodal forms into the pure enantiomers. Instantaneous racemization occurs, however, after deprotonation of the ammonium salt. At the very moment of its formation, the resulting amine has still preserved the original spatial orientation of its substituents. But since it disposes of a very efficient mechanism to accomplish the inversion of its shape, its configurational homogeneity is rapidly lost. At the expense of some 6 kcal/mol, a typical trialkylamine can flatten its pyramidal ground state shape and reach a trigonal planar transition state (1) from which it may revert to the original geometry or cross over to its mirror image. In other words, on deprotonation a quaternary nitrogen center loses its configurational stability.

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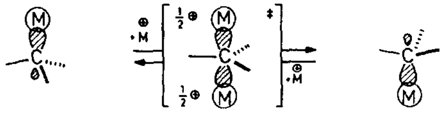
When we now extrapolate back from amines to organometallics, the fictitious carbanion can help us to evaluate the role of the central atom. If the electronegative nitrogen is replaced by a carbon atom, the attractive forces between the nucleus and the non-bonding electrons will diminish. Consequently, the latter can be more easily accomodated in a more distant p- rather than in an s-hybridized orbital. According to *ab initio* calculations, the activation energy for the pyramidal inversion of a counterion-free methyl anion is negligibly small (about 1 kcal/mol) [2].

Sooner or later, however, we have to face reality, and this means the existence of an organometallic species with a carbon-metal bond. There is no simple way to get the metal from above to below the plane. While the electron density can flow through the node at the carbon atom in a most straightforward manner, the metal must physically travel around the entire anion until it arrives at its new binding site. This would imply a complete ionization of the organometallic bond and this should be unrealistic for energy reasons. There remains, as the only plausible hypothesis, the assumption of a replacement of the metal by another metal approaching from the rear (transition state **2**) rather than from the front side as is common with bimolecular electrophilic substitutions. It is difficult to evaluate the activation required for such a process. It appears to be small in general, since optically active *sec*-alkyllithium compounds have been found to racemize rapidly even at temperatures around -75 °C [3].



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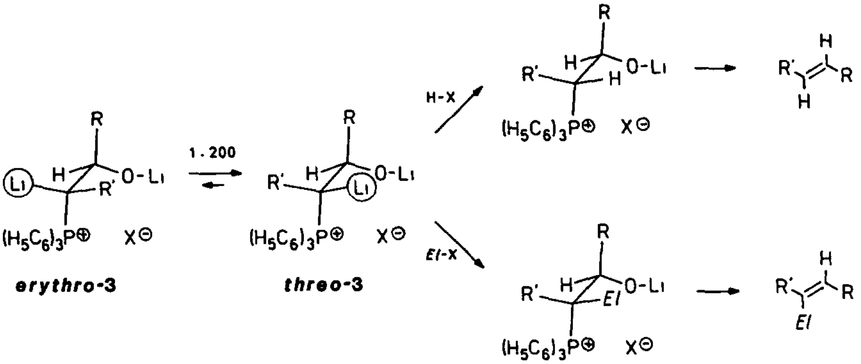
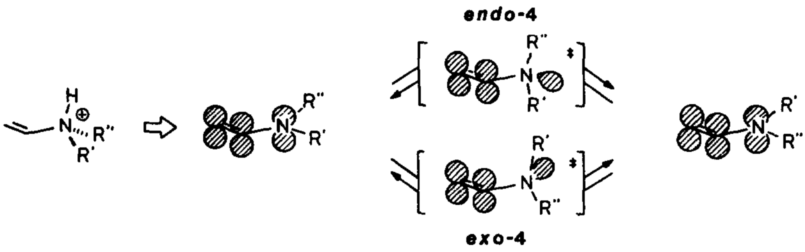
Racemization is, of course, unfortunate. Nevertheless, the possibility to promote a rapid configurational inversion offers a very convenient means to convert a mixture of diastereomers into a single stereoisomer provided there is a substantial difference in the thermodynamic stabilities of the two components. This strategy was successfully applied for the first time in the area of stereoselective Wittig reactions [4]. When a (triphenylphosphonio)alkanide, a so-called "reactive" phosphorus ylid, is allowed to combine with an aldehyde in the presence of soluble lithium salts, the resulting betaine-LiX adducts (shown overleaf) are obtained as *erythro*/*threo* diastereomers in proportions usually ranging from 1 : 1 to 3 : 1. Subsequent treatment of this mixture with phenyllithium or another strongly basic organolithium reagent generates the "betaine ylid" **3** as the key intermediate. If available in sufficient concentration, a lithium cation binds to the carbanionic α-center of this β-lithiooxy ylid and thus makes it tetragonal. Now virtually instantaneous epimerization by pyramidal inversion takes place even at very low temperatures (*e.g.*, at -80 °C). At equilibrium, the *threo* form proves to be heavily preponderant, typical *erythro*/*threo* ratios being 0.5 : 99.5. Reprotonation leads back to the *threo* betaine which is the immediate precursor to the *trans* olefin. Reaction of the betaine ylid with an electrophile *El*-X rather than an acid, produces an α-substituted betaine which, upon elimination of triphenylphosphine oxide, gives rise to a stereochemically pure trisubstituted ethylene having a predictable configuration ("SCOOPY method" or "three-dimensional Wittig reaction") [4].



2.2. The Torsional Isomerization of Allylmetal Compounds

The carbonucleophilic essence of a 2-alkenylmetal compound is the implied allyl anion, the isoelectronic nitrogen analogue of which is the uncharged aminoethylene, the simplest enamine. Due to the resonance interaction of the lone pair electrons with the adjacent olefinic π-bond, the pyramidal configuration around the nitrogen atom is much flattened, to the extent of being almost planar. Therefore, the inversion of this center is immeasurably fast.

On the other hand, the same σ,π-interaction slows the torsional motion around the α-carbon-nitrogen bond. Since the conjugation provides a resonance stabilization of approximately 10 kcal/mol, this amount of energy has to be sacrificed before the carbon-nitrogen bond can be twisted. Moreover, while in the ground state the hetero center is virtually planar, it repyramidalizes after the delocalizable electrons have been disconnected. Therefore, there are two transition states, *endo*-**4** and *exo*-**4**, which accommodate the nitrogen lone pair, either looking inward or outward, in the same plane as the heavy atoms of the enamine moiety, while the olefinic π-system maintains its orthogonal orientation. Presumably their free enthalpies, and hence the activation barriers separating them from the ground state, are of comparable size. Once at the transition state, the molecule may revert to its former geometry or continue the rotation to 180° until the parallel alignment of the resonance active orbitals is again achieved. This time, however, the two substituents R' and R" have exchanged their chemical environments : that which had previously occupied the *endo* position is flipped over to the *exo* position, while the substituent that started out there appears at the *endo* site.



If the enamine nitrogen were protonated, the barrier hindering the C^{α},N rotation in such a hypothetical vinylammonium salt would be negligibly small ($E_{\alpha} \sim 2$ kcal/mol), *i.e.*, of the same magnitude as in any saturated amine. This time, clearly, deprotonation has had the effect opposite to that in the previous case of pyramidal inversion. If torsional isomerization processes are considered, it reduces the internal mobility.

Let us turn now to metal derivatives of allyl species. The statics and dynamics of their structures have many fascinating facets. There is, first of all, the question of the nature of the carbon-metal bond. Allylic Grignard reagents (*e.g.*, **5**) exhibit a conventional structure having a monohapto (η^1) σ-bonded carbon-metal linkage, as do allyl compounds of most other metals (*e.g.*, diallylmercury **6**). In contrast, alkali metals as well as many heavy transition elements establish a trihapto (η^3) π-bonded interaction with the carbon backbone [5]. However, due to its smallness, the lithium extends a somewhat shorter and a somewhat longer bond to the two allylic termini of allyllithium (**7**) [5, 6]. In contrast, allylsodium (**8**), allylpotassium and allylcesium (**9**) form perfectly symmetrical π-complexes [6, 7].

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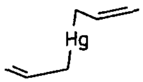

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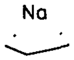

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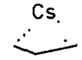

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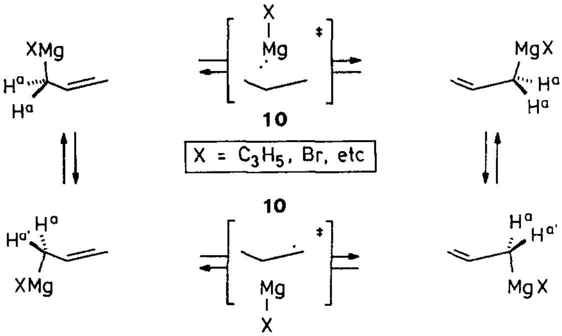
Depending on their nature and on the solvent used, η^1 and η^3 organometallics may form dimeric, trimeric, tetrameric, hexameric of even polymeric clusters, so-called "aggregates" [7]. In order to restore free rotation around one of the allylic carbon-carbon axes, first of all the aggregates might have to be dissociated into monomers. Whether this is really indispensable and how much energy has to be supplied for this process, is as yet unknown. Next, η^3 have to be converted into η^1 structures. In general, only a modest amount of energy should be required for this transition. Finally, the allylic resonance has to be abandoned. How much stabilization energy is lost in that way depends on the metal involved. The two extreme cases are propene, the "hydrogen derivative", with zero delocalization and the counterion-free allyl anion with a resonance stabilization of approximately 25 kcal/mol [8]. In real allylmetal compounds the carbanionic lone pair may be used either to construct a σ-bond to the metal or be "diluted" by sharing the electron excess between the two terminal positions. In the latter case, resonance energy is gained, but the binding of the metal is weakened. The two conflicting options are reconciled in a compromise : electronegative metals retain most, though not all, of the electron density in order to establish a strong bond; electropositive ones allow a substantial fraction of it to flow to the vinylogous position. Despite the bulkiness of the metal, dialkylmercury has a homoeopolar, covalent bond. Although a parallel alignment of the latter with the adjacent olefinic p-orbitals appears to be maintained [9], the gain in resonance energy is very small as evidenced by the nmr equivalence of the allylic hydrogens even at very low temperatures ($ABCX_2$ spectrum) [10]. It must be still small in diallylmagnesium [11] and allylmagnesium bromide [12], since again the rotation around the C(1),C(2) bond cannot be frozen out ($E_a \sim 5$ kcal/mol ?). In addition, another fast exchange process is observed : the rapid oscillation of the metal between the two allylic termini. This metallotropic process, which is mediated through a π-bonded transition state **10**, averages all terminal hydrogen atoms on the nmr time scale. In this way, an AB_4 spectrum is observed at higher temperatures.



The degeneracy of the two metallomers is removed when methyl groups are introduced on one side of the allyl moiety. The nmr spectrum of 3-methyl-2-butenylmagnesium bromide ("prenylmagnesium bromide") shows a sharp singlet for both methyl groups at 25 °C but two methyl resonances below -10 °C. Line shape analysis suggests a torsional barrier in the order of 10 kcal/mol. The persistent equivalence of the methylene hydrogens even at low temperatures as well as the ^{1}H [13] and ^{13}C [5] chemical shifts leave no doubt as to which metallomer is thermodynamically favored : the prenylmagnesium (**12**) must considerably predominate over the 1,1-dimethylallylmagnesium form (**11**).

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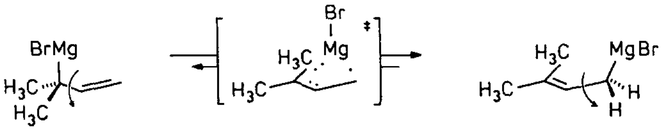

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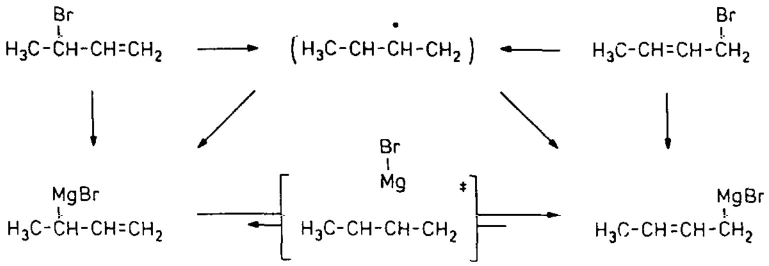
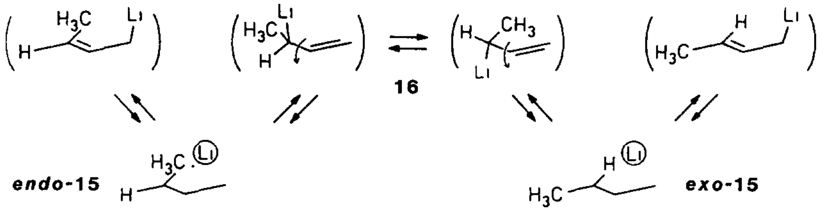
The metallomeric mobility of allyl type Grignard reagents has practical consequences. Regardless of the precursor, 1-methylallyl or 2-butenyl bromide, insertion of magnesium produces the same Grignard reagent. According to all the evidence, it exists in the crotyl form **14**, the species **13** carrying the metal at the inner terminus of the allyl moiety again being present only in minute, undetectable concentrations. Furthermore, it does not matter whether or not stereochemically homogeneous starting materials are employed. Due to rapid torsional isomerization, the crotylmagnesium compound invariably emerges as a *cis/trans* mixture.



13 **14**

Allyllithium (7) in tetrahydrofuran displays an ABB'CC' spectrum at -90 °C, which simplifies to an AB_4 pattern above -30 °C [11]. Activation parameters of E_a 11 kcal/mol and A 10^{13} have been derived from the temperature dependence of the exchange phenomenon. A similar ABB'CC' ⇔ AB_4 transition had been previously reported for diallylzinc [14]. However, unlike allyllithium, the latter compound appears to favor a σ-bonded (η^1) metal-carbon backbone interaction.

Crotyllithium (**15**) can readily be generated by reductive cleavage of *trans*-2-butenyl phenyl ether [15]. Due to rapid torsional isomerization via the secondary metallomer **16**, however, one obtains a dynamic mixture of *cis* ("*endo*") and *trans* ("*exo*") isomers, the proportions of which vary from 1 : 1 to 3 : 1 as a function of the solvent [15].



16

***endo*-15**

***exo*-15**

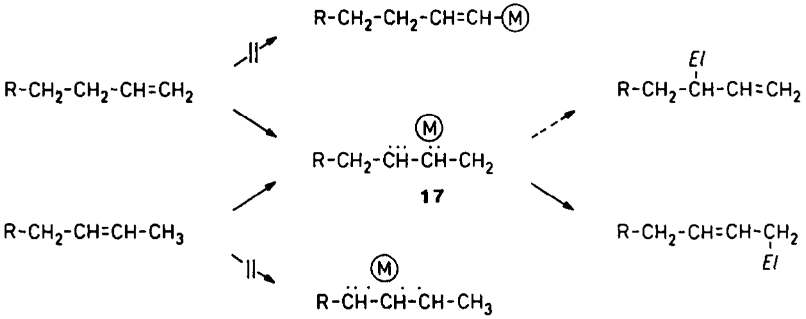
The torsional barriers increase substantially if lithium is replaced by a heavier alkali metal. For example, with allylpotassium it reaches 17 kcal/mol, which corresponds to a coalescence temperature of 68 °C for the ABB'CC' ⇔ AB_4 transition [16]. Rotation around the C(2),C(3) axis of 2-alkenylpotassium and -cesium compounds is even more restricted. This "slow motion" torsional mobility has become the key to control over the geometry of allyl type organometallics and, on this basis, to novel strategies for stereoselective synthesis.

3. THE STEREOCHEMISTRY OF 2-ALKENYLMETAL COMPOUNDS

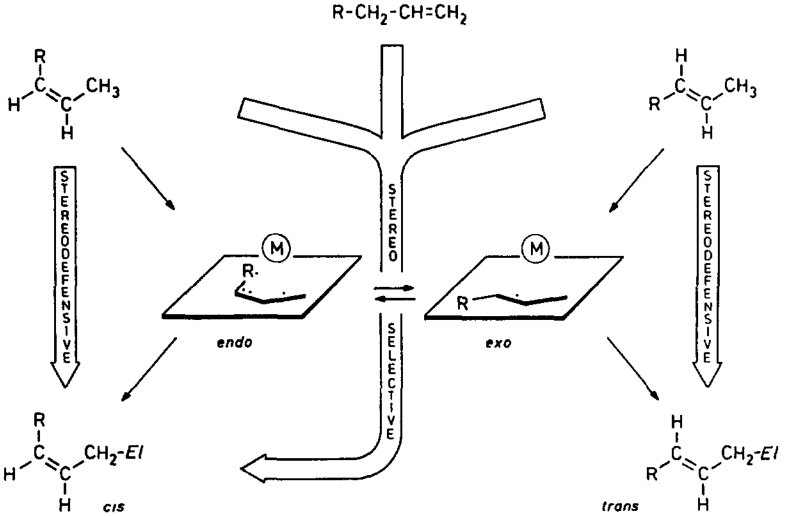
In the following sections we have to differentiate between *stereoconservation (stereodefence, stereoresistance)* and *stereoselection (stereopreference)*. 2-Alkenylpotassium reagents offer us both options. They may be generated from stereoisomerically well-defined precursors under conditions which assure complete retention of the original configuration. Alternatively, they may be allowed to undergo torsional *(Z/E)* or *endo/exo* equilibration. Stereochemical homogeneity can also be achieved in this way, since frequently one of the alkenylpotassium isomers is thermodynamically much more stable than the other.

3.1. Allyl Species

The superbasic mixture of butyllithium and potassium *tert*-butoxide reacts with olefins containing allylic CH bonds to give smooth and almost quantitative hydrogen/metal exchange ("metalation"). The process is *typoselective* ("chemoselective"), *regioselective* and *stereoselective* : no nucleophilic addition to the double bond, but only proton abstraction is observed; always considering allylic positions, methyl is much more readily attacked than methylene, not to speak of methine groups; and *cis* olefins react faster than the corresponding *trans* isomers [16, 17]. In this way, highly nucleophilic 2-alkenylmetal compounds 17 (M = K, Li) are obtained from both 1- or 2-alkenes. They are essentially potassium derivatives, although they still contain small amounts of lithium unless the latter component is extracted by repetitive washing operations [18]. Such intermediates have proven to be very reactive towards a wide variety of electrophiles. Moreover, they exhibit a synthetically valuable regioselectivity : electrophiles get preferentially attached to the unsubstituted terminal position to afford the chain elongated products. This contrasts with the propensities of allylic lithium or magnesium compounds, which form mainly or exclusively the branched isomers derived from electrophilic substitution at the inner end of the allyl moiety [19].



Most remarkable is the stereochemical behavior of 2-alkenylpotassium compounds prepared by superbase metalation of pure *cis* or *trans* alkenes. Since the deprotonation does not affect the configuration of the unsaturated carbon backbone, a *cis*-2-alkene will inevitably lead to an *endo*-alkyl substituted allylmetal species while an *exo*-alkyl stereoisomer must result from a *trans*-olefinic precursor. If, immediately after its formation, the intermediate is quenched with a suitable electrophile, the initial configuration is fully retained. In this way, a ***stereodefensive*** reaction sequence can be performed that delivers the original *cis* or *trans* double bond intact to the final product.



Alternatively, the 2-alkenylpotassium intermediate may be submitted to torsional isomerization under thermal [16, 17] or catalytic conditions [20]. Under these circumstances it no longer matters whether a *cis* or *trans*-2-alkene or a 1-alkene, or even a mixture of such isomers, was used as the starting material. As long as the substituent R is a methyl or primary alkyl group, the *endo* isomer is thermodynamically strongly favored and will be the preponderant component after equilibration. Irrespective of the nature of the precursor, the final derivative will contain a *cis* double bond, and hence a *stereoselective* reaction sequence has been accomplished.

In order to quantify the stereopreferences of 2-alkenylpotassium reagents as a function of the substituent R and the metal M, the *cis* and *trans* isomers of 2-butene, 2-pentene (sometimes replaced by 2-hexene or 2-octene), 4-methyl-2-pentene and 4,4-dimethyl-2-pentene were submitted to superbase metalation. The *endo/exo* compositions of the resulting organometallic intermediates **17** (see Table 1) were determined by ^{13}C-nmr spectroscopy or, more accurately, by correlation with the *cis/trans* ratios of the derivatives obtained after reaction with a reliable electrophile known to give high yields of products and to exhibit high regioselectivity in favor of the terminal attack [16, 17]. In this way, *endo*- and *exo*-2-butenylpotassium were found to be present at equilibrium in the ratio of 124 : 1. When the methyl substituent is replaced by an ethyl or another primary alkyl group, the *endo/exo* ratio drops to 15 : 1 and with the branched isopropyl group to 5 : 1. The doubly branched *tert*-butyl group even reverses the relative stabilities, the *endo* conformer becoming now disfavored to the extent of 1 : 10 [16, 17, 21]. (With a trimethylsilyl group, the *endo/exo* ratio approximates to 1 : 20 [17, 22, 23], while with the even bulkier triphenylmethyl substituent the two stereoisomers were found to coexist in equal amounts [24]). However, we have to oppose this ratio to the *cis/trans* equilibrium ratio of 1 : 10000 estimated for the corresponding hydrocarbon, 4,4-dimethyl-2-pentene, on the basis of the reported enthalpy differences between the two stereoisomers. Thus, when compared with their olefinic precursors, all (*Z*)- or *endo*-2-alkenylpotassium species enjoy a bonus of some 2 - 3 kcal/mol relative to their *(E)* or *exo* isomeric counterparts. In this way, an unprecedented though quite general type of interaction is identified.

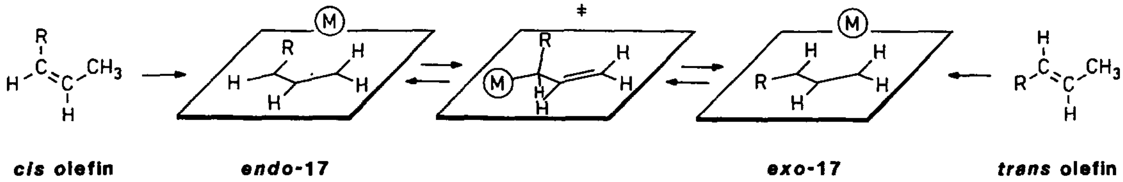


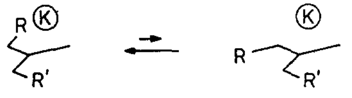
Table 1. Torsional equilibration of 2-alkenylmetals (**17**) and, for comparison, the corresponding alkenes : *endo/exo (Z/E)* ratios (in round figures).

M =	H	Li	Na	K	Cs
R = H_3C	1 : 5	2 : 1	10 : 1	100 : 1	500 : 1
R = H_3C-CH_2	1 : 5			15 : 1	
R = $(H_3C)_2CH$	1 : 5			5 : 1	
R = $(H_3C)_3C$	1 : 10 000			1 : 10	

Solvent effects on the *endo*/*exo* ratios are generally moderate. On the other hand, the *endo* preference increases steeply with the electropositivity of the metal (see Table 1). While the two stereoisomers of crotylmagnesium bromide are of equal stability, no trace of *exo*-2-butenylcesium is detected after torsional equilibration.

The introduction of an additional methyl or primary alkyl group into the 2-position, the nodal point, of the allyl moiety has no electronic effect. It causes, however, a slight steric repulsion if the other alkyl substituent occupies the terminal *exo* position. Since no such interaction affects the *endo* form, the *exo* isomer becomes even more disfavored than in the previous cases. A series of 1,2-dialkyl-substituted allylpotassium compounds has been prepared by metalation of the appropriate olefin either with the butyllithium/potassium *tert*-butoxide reagent or with trimethylsilylmethylpotassium [25]: 2-methyl-2-butenylpotassium [**18a**: R = H_3C, R' = H], 2-methyl-2-pentenylpotassium [**18b**: R = H_5C_2, R' = H], 2-methyl-2-heptenylpotassium [**18c**: R = H_9C_4, R' = H], 2-ethyl-2-heptenylpotassium [**18d**: R = H_9C_4, R' = CH_3] and 2,4,4-trimethyl-2-pentenylpotassium [**18e**: R = $(H_3C)_3C$, R' = H]. After equilibration, typical *endo*/*exo* ratios ranged from 50 : 1 to 500 : 1 [26].

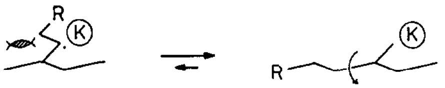
endo-18



exo-18

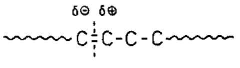
At first sight, there should not be much discrimination between a methyl and a primary alkyl group which, both located at the same terminal position of the allyl moiety, compete for the more "comfortable" *endo* position. A closer look, however, reveals a *syn* arrangement of 1,4-centers in the (*Z*) isomers, while the *(E)* isomer can avoid such unfavorable interactions due to its greater conformational mobility. Actually, we were able to generate two representative organopotassium species **19a** [R = H_3C] and **19b** [R = $(H_3C)_2CHCH_2$] by metalation of 3-methyl-1-hexene and 3,7-dimethyl-1-octene ("dihydrocitronellene"), respectively, with trimethylsilylmethylpotassium. Their torsional isomerization required mercury or magnesium salt catalysis until the final *(Z/E)* equilibrium position of 9 : 91 was reached [27].

Z-19

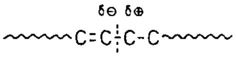


E-19

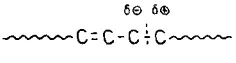
The stereocontrolled generation of 2-alkenylpotassium compounds opens a new route that optionally leads to *cis* or *trans* unsaturated substances. This novel approach is complementary to two older ones : condensation of an allyl type organometallic reagent with a suitable carboelectrophile creates a new carbon-carbon bond between the allylic and the homoallylic position, while the alkylation of an acetylide links a future olefinic to a future allylic carbon atom and the Wittig reaction assembles two organic moieties around the double bond itself.



via phosphorus ylids

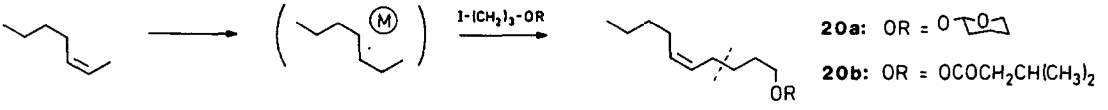


via acetylenes

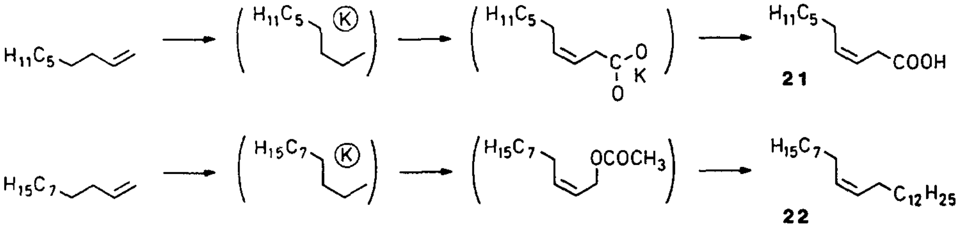


via allylpotassium intermediates

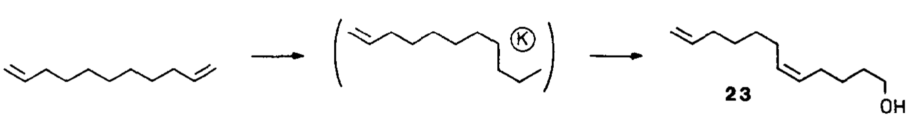
A few syntheses of pheromones, the chemical signals of insects, may illustrate the potential of the alkenylpotassium approach. After consecutive treatment of *cis*-2-heptene with the butyllithium/potassium *tert*-butoxide ("LICKOR") mixture and 3-(2-tetrahydropyranyl)propyl iodide an acetal (**20a**) was obtained. This was hydrolyzed and esterified with isovaleroyl chloride to afford the sex attractant **20b** (31%) of female *Nudaurelia cytherea cytherea*, the pine emperor moth. Ester **20b** was separated chromatographically from the branched regioisomer present as a minor by-product [28].



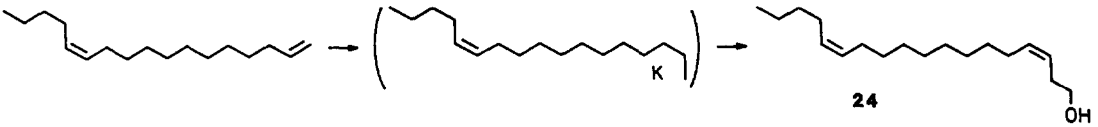
After this example featuring a stereodefensive reaction sequence, a few stereoselective syntheses will be described. The intermediate obtained by the superbase metalation of 1-nonene is allowed to undergo torsional equilibration before being poured on dry ice. After neutralization and crystallization, pure (*Z*)-3-decenoic acid (**21**, 38%), a pheromone of the virgin furniture carpet beetle *Anthrenus flavipes*, was isolated [28]. Similarly, 1-undecene was converted *via* the 2-alkenylpotassium intermediate into (*Z*)-2-undecen-1-ol [28]. The acetate was then submitted to the copper catalyzed coupling [29] with dodecylmagnesium bromide to afford (*Z*)-9-tricosene ("muscalure", **22**, 77%), the sex attractant of the common house fly *Musca domestica* [30].



By the appropriate choice of the solvent, 1,(ω-1)-dienes can be submitted to selective mono- or dimetalation [31]. Consecutive superbase metalation of commercial 1,10-undecadiene in tetrahydrofuran, catalytic *(Z/E)* equilibration, condensation with 3-(2-tetrahydropyranyl)propyl iodide, hydrolysis of the acetal function and, finally, fractional crystallization (to get rid of the branched regioisomer) gave (*Z*)-5,13-tetradecadien-1-ol (**23**, 17% over-all), the alcohol as well as its acetate being major components of the mandibular secretion of *Cossus cossus* (goat or carpenter moth) larvae [31].



The readily accessible 1,12-heptadecadiene has three allylic and hence relatively acidic positions. Since all of them are occupied by a methylene group, one may worry about the possibility of random deprotonation. As expected [32], however, metalation takes place selectively at the allyl position adjacent to the vinyl group. Reaction of the organometallic intermediate with paraformaldehyde produced a 2 : 3 mixture of the branched and chain elongated regioisomers. The main component, (3Z,13Z)-3,13-octadecadien-1-ol (**24**, 22%), which was purified by repetitive low temperature crystallization. It has been previously identified as the sex attractant of *Sanninoidea exitiosa*, the peach tree borer moth [31].



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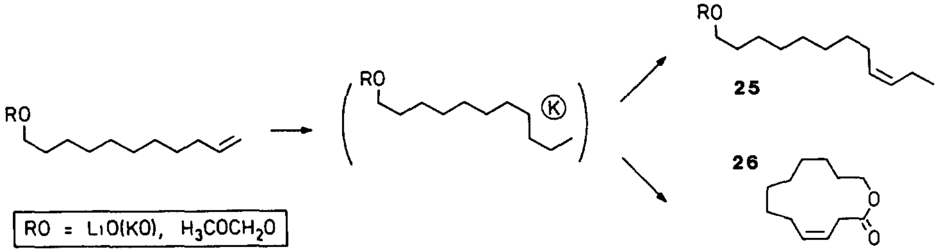
Use of 10-undecen-1-ol as starting material has led to two different pheromones. Metalation of the alcoholate or of the *O*-methoxymethoxy protected alcohol generated an organopotassium intermediate which could be alkylated with methyl iodide to give (Z)-9-dodecen-1-ol (**25**, 69%), the acetate of which is the main semiochemical of the female grape berry moth *Paralobesia viteana* [28]. Treatment of the organometallic intermediate with carbon dioxide followed by cyclization afforded (Z)-3-dodecen-12-olide (**26**, 40%), a pheromone component of the flat grain beetle *Cryptolestes pusillus* [33].



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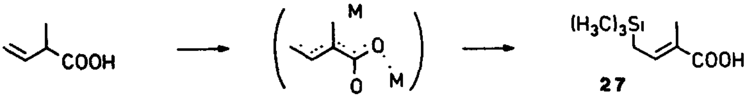
In analogy to unsaturated alcohols, unsaturated carboxylic acids also undergo metalation at an allylic position if the acid is first converted into a metal carboxylate. Consecutive treatment of 2-methylbut-3-enoic acid with the LICKOR reagent, chlorotrimethylsilane and water gave (*E*)-2-methyl-4-(trimethylsilyl)but-2-enoic acid (**27**, 51%) as the sole product [33].



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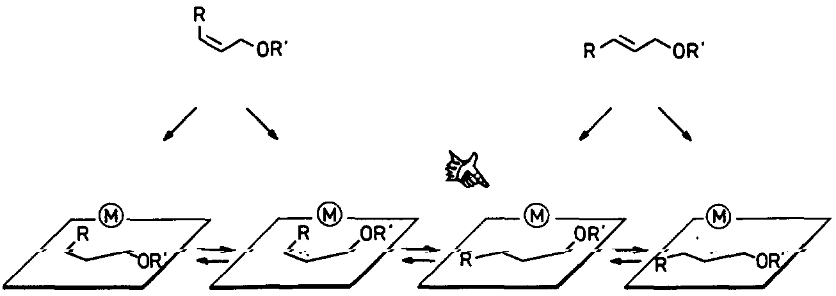
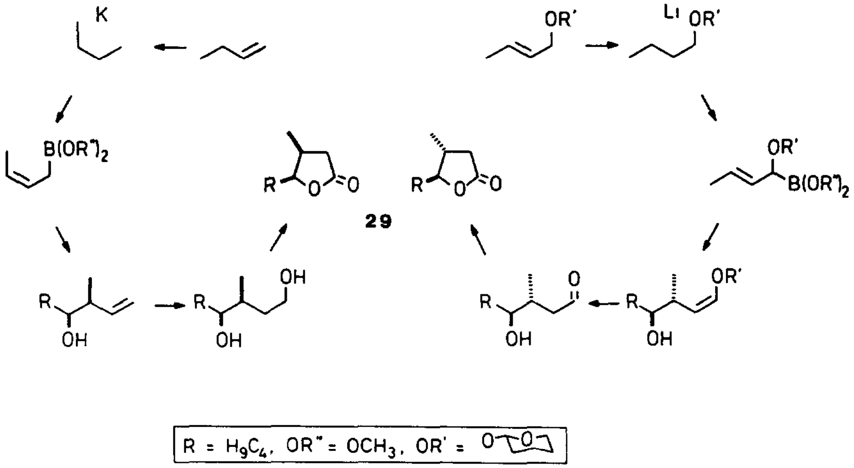
The superbase metalation of allyl ethers and allyl thioethers is very easy [34]. Crotyl ether derived intermediates show high torsional mobility and favor the *endo*-alkoxy *exo*-alkyl conformer (*endo*-OR'-*exo*-R-**28**) apparently exclusively, regardless of whether lithium or potassium is used as the metal [35].



***endo*-OR'-*exo*-R-28**

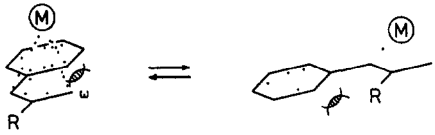
Allyl type organometallics can be smoothly condensed with fluorodimethoxyborane to afford dimethyl alkeneboronates and, after oxidation with hydrogen peroxide in alkaline medium, allyl alcohols [36]. Like other allyl [37] or enolate [38] type boron compounds, these boronates can also be employed in highly stereoselective nucleophilic addition reactions to aldehydes. If the alkyl group resides in the *cis* position, a *threo* adduct results; the *trans* isomer produces an *erythro* adduct. The superbase approach allows the creation of such geometries at will.

A sequence of transformations also involving *endo*-OR'-*exo*-CH_3-**28** (OR' = 2-tetrahydropyranyloxy) was used to prepare the *cis* and *trans* isomers, respectively, of the so-called "oak lactone" (or quercus lactone **29**, R = H_9C_4) quite readily [35]. Asymmetric induction towards very high diastereoselectivities and enantioselectivities can be achieved with boranes carrying two homochiral alkoxy groups in addition to the allyl moiety. The e.e. values reported for pinene derived reagents average 95% and in favorable cases attain 99% [39].



3.2 Arylallyl Species

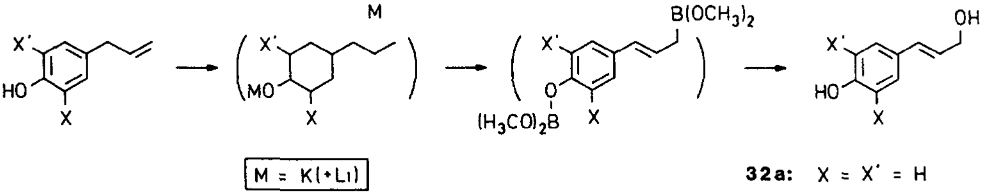
The replacement of the 1-alkyl substituent in 2-alkenylmetal intermediates by a phenyl or aryl moiety results in a considerable extension of the area of delocalization and, consequently, an increase in resonance stabilization. However, perfect coplanarity, a prerequisite for optimum electron distribution, is only possible if the aryl substituent is accomodated in the *exo* position. Due to repulsive overlap of *ortho*- and ω-hydrogen atoms, the aromatic ring in the *endo* isomer of phenylallylmetal **30** is rotated out of the allyl plane, a twist angle of 30° being probable. The *exo* form is indeed found to be favored, as deduced from the *cis/trans* composition of final the products obtained after carboxylation [40] or conversion into the acetate by consecutive treatment with fluorodimethoxyboron, alkaline hydrogen peroxide and acetic anhydride [41]. Nevertheless, a substantial amount of the *cis* isomer was also formed regardless of whether the metalation was carried out with the LICKOR superbase or with trimethylsilylmethylpotassium. The proportion varied with the solvent : in hexane a *cis/trans* ratio of 5 : 95, in tetrahydrofuran of 14 : 86 and in diethyl ether of 0.5 : 99.5 was found. The latter number could be spurious due to precipitate formation. Phenylallylpotassium (**30**, M = K) being fairly insoluble in diethyl ether, the torsional equilibrium is perturbed by the precipitation of one of the components [41]. The *cis/trans* ratio monitored for products derived from phenylallyl*lithium* (**30**, M = Li) falls in the range between 6 : 94 and 7 : 93 with any kind of ethereal solvent [41].



30: R = H
31: R = H_3C

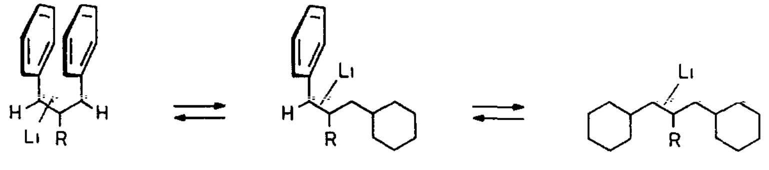
Introduction of a methyl (or other alkyl) group at the 2-position completely reverses the relative stabilities of both the lithium (**31**, M = Li) [42] and the potassium compound (**31**, M = K) [41]. Metal invariant *cis/trans* ratios of 99 : 1 or 95 : 5 were determined depending on whether the intermediates were trapped in an ethereal solution or in hexane suspension.

As an application of these findings, the readily available allylarenes chavicol (X = X' = H), eugenol (X = H_3CO, X' = H) and 5-allylpyrogallol 1,3-dimethyl ether (X = X' = H_3CO) were metalated with the LICKOR reagent in tetrahydrofuran at -95 °C and the intermediates treated with fluorodimethoxyboron followed by alkaline hydrogen peroxide. The three lignin building blocks coumaryl, coniferyl and sinapyl alcohol (**32a**, **32b** and **32c**, respectively) were isolated from the one-pot reaction mixture in 76 - 81% yield as pure *(E)*-isomers [43]. Possibly the torsional equilibrium is again displaced because of poor solubility of the *(E)* component.



32a: X = X' = H
32b: X = H_3CO, X' = H
32c: X = X' = H_3CO

The 1,3-diphenylallyllithium species **33** can exist in *endo/endo*, *endo/exo* and *exo/exo* forms. In the unsubstituted parent compound (**33a**; R = H) the *exo/exo* form is strongly favored, although trace amounts of the *endo/exo* isomer are detectable. The introduction of increasingly bulkier alkyl or aryl substituents into the 2-position shifts the torsional equilibrium first to the *endo/exo* and, finally, to the *endo/endo* side (see Table 2) [44].



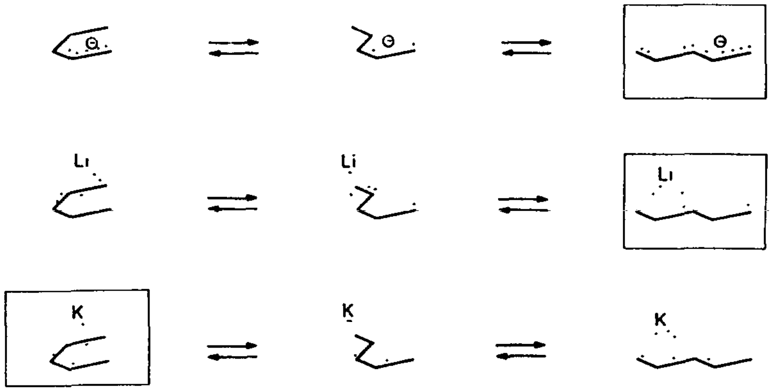
endo/endo-33 **endo/exo-33** **exo/exo-33**

Table 2. 1,3-Diphenylallyllithium species **33** : position of the torsional equilibrium as a function of the substituent R [44].

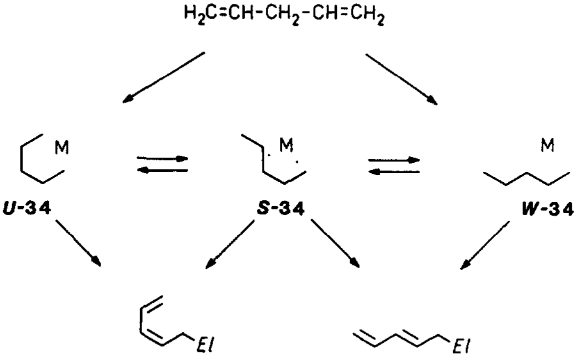
R	*endo*/*endo*		*endo*/*exo*		*exo*/*exo*
H	0	:	8	:	92
CH_3	0	:	92	:	8
CH_2CH_3	17	:	68	:	15
C_6H_5	44	:	56	:	0
$CH(CH_3)_2$	62	:	38	:	0
$C(CH_3)_3$	100	:	0	:	0

3.3 Pentadienyl and Heptatrienyl Species

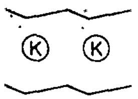
When a vinyl group is attached to the terminal position of an allyl system, again both structural elements should be placed in the same plane in order to gain a maximum of extra resonance energy. This restricts the vinyl moiety to two conformations when accomodated at an *endo* and again two when located at an *exo* site. In either case it can be twisted inward or outward. The *endo-outward* and the *exo-inward* conformers, however, are degenerate. Thus, a set of three coplanar, hence optimally resonance stabilized pentadienyl species results : the horseshoe like *U* shape, the sickle like *S* shape and the zigzag-band like *W* shape. The *W* form is free of steric strain and the electron density is distributed over a maximum distance. Therefore, it will be undoubtedly favored as long as we deal with counterion-free carbanions. In the condensed phase, however, most pentadienylmetal compounds form tight contact species rather than ion pairs, let alone dissociated ions. The binding interaction of a lithium cation with the pentadienide backbone should not alter the overall picture : again we conclude that the *W* shape should be the preferred conformer. Only with bigger metals such as potassium and cesium does a new factor come into play. Their greater atomic radii allows them to span from one terminus of the pentadienyl moiety to the other provided the latter coils up to adopt the *U* shape. In this way, a pentahapto (η^5) binding interaction can be established that holds the "open sandwich" structure together.



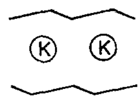
Such qualitative considerations have proved to be correct. When 1,4-pentadiene was deprotonated with *sec*-butyllithium and the intermediate was subsequently trapped with a suitable electrophile, only *(E)*-penta-2,4-dienyl derivatives were obtained [45]. This result is in perfect agreement with an earlier structural assignment of pentadienyllithium to which the *W* shape (*W*-**34**) was attributed on the basis of nmr coupling constants [46]. In contrast, pentadienylpotassium in tetrahydrofuran gives rise to (*Z*)-2,4-pentadienyl derivatives and therefore must have the *U* shape (*U*-**34**) [45, 47]. Again this structural inference was corroborated by nmr spectroscopic data [48]. In neither case is there any serious contamination by the *S* form (*S*-**34**). The latter would inevitably produce a mixture of stereoisomeric products.



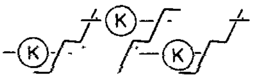
Strangely enough, pentadienylpotassium generated by superbase metalation of 1,4-pentadiene in hexane produces *(E)*-configurated derivatives. A tentative explanation suggests that the organopotassium compound forms stretched-out dimers **35**, if not higher oligomers or even polymers (**36**), in non-ethereal hydrocarbon media [45].



***syn*-35**

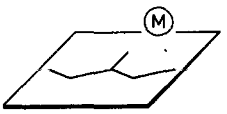


***anti*-35**



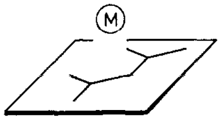
36

Whatever the solvent, both 3-methyl-2,4-pentadienyllithium (**37**, M = Li) and -potassium (**37**, M = K) show a distinct preference for the *W* shape [45]. The *endo* preference described above may be at the origin of this stereochemical behavior. Only the *W* shape can accomodate the methyl group of intermediate **37** in a double *endo* position. The opposite is true for 2,4-dimethyl-2,4-pentadienyllithium (**38**, M = Li) and -potassium (**38**, M = K) which both favor the *U* shape of the dienide backbone. Being attached to the nodal points, the methyl groups should not exert any major electronic effect. On the other hand, they would built up serious steric strain by mutual repulsion if located in the *W* form, especially since they would have to point towards each other due to the well-known widening [5, 49] of the central angle (to some 130 °) in the allyl anion and its metal derivatives [45].



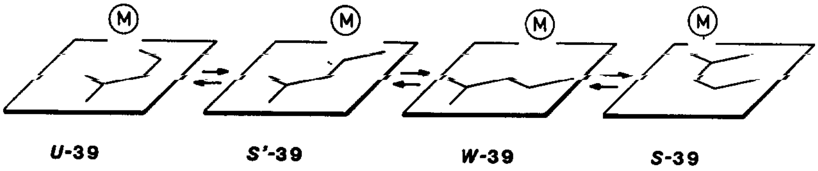
37

M = Li, K

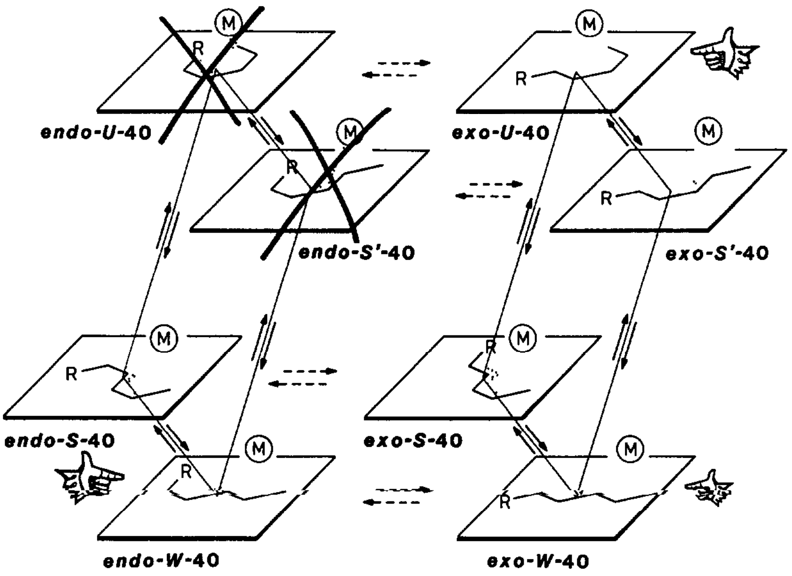


38

If just a single methyl substituent is linked to the pentadienyl backbone the hitherto prevailing degeneracy of the *S* shape is removed. The substituent may show up at the blade or at the handle of the sickle. Thus, we face now a choice of four coplanar structures, the *U*, *S*, *S'* and *W* forms. Fortunately, the sickle shapes again do not qualify as viable conformers. As the parent compound **34**, 2-methyl-2,4-pentadienyl-lithium (**39**, M = Li) and -potassium (**39**, M = K) exist in the *W* and the *U* shape, respectively [45].

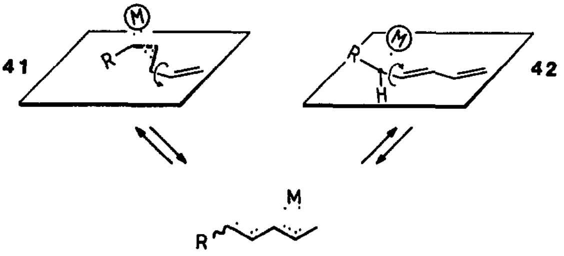


Shifting the alkyl group to the terminal position again increases the conformational manifold. In fact, an 2,4-alkadienylmetal compound (**40**) now has the additional choice of placing the substituents in the *endo* and the *exo* positions. Two out of the eight *formally* coplanar conformers can be ruled out as unrealistic because of severe transannular overlap : the *endo-U* form and the *S'* form carrying the *endo*-substituent at the blade of the sickle. Three of the remaining six conformers can now be selected to become the most densely populated, if not the exclusive, species. Two variable parameters suffice to achieve the desired conformational control : the metal, whether lithium or potassium, and the stereochemistry, whether *cis* or *trans*, of the hydrocarbon precursor.

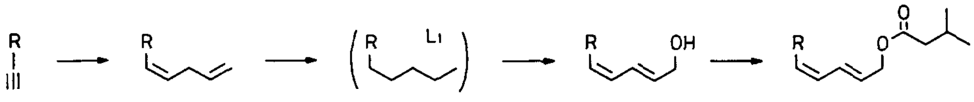


It does not matter whether a (2*Z*,4*Z*)-2,4-, a (2*E*,4*Z*)-2,4- or a (*Z*)-1,4-alkadiene is used as the starting material. In each case deprotonation with *sec*-butyllithium generates the pure *endo-W*-**40** species. On the other hand, metalation of a (4*E*)-2,4- or -1,4-diene with *sec*-butyllithium in the presence of potassium *tert*-butoxide produces the *exo-U*-**40**, again with very satisfactory stereoselectivity (better than 97%, and presumably about 99%) [50]. Only moderate stereochemical uniformity is achieved if *sec*-butyllithium alone is used as the reagent. Two organometallic conformers are formed in a 9 : 1 ratio, *exo-W*-**40** as the major and, presumably, *exo-S*-**40** as the minor component [50].

These results imply that the free passage from the (4Z) to the (4*E*) series and back is blocked under ordinary experimental conditions. This is quite reasonable. As we have seen previously, the torsional isomerization around the C(2),C(3) bond of a 2-alkenylpotassium species requires some 20 kcal/mol. This is essentially the price to be paid for sacrificing the allyl resonance. When we turn now to 2,4-alkadienylmetal species we have to differentiate between "inner" C,C-bonds, *e.g.*, the C(2),C(3) axis, and "outer" C,C-bonds, *e.g.*, the C(4),C(5) axis. Rotation around an inner bond (transition state **41**) requires only that delocalization into the vinyl wing is prevented. The reduction of delocalization from a pentadienyl to an allyl system should hardly cost more than 10 kcal/mol. If, however, torsional isomerization should occur at an outer C,C-bond (transition state **42**), the entire resonance energy, estimated to be worth at least 30 kcal/mol, would be lost. This amount of energy is not available at ordinary or lower temperature [50].



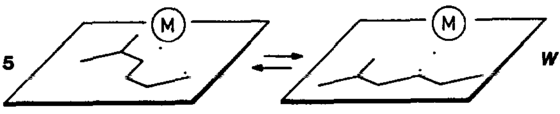
All unbranched 2,4-alkadienylmetal species, including the hexadienyl parent system, appear to have the same stereochemical characteristics. It is mainly for analytical convenience that most studies have been carried out with long chain model compounds, notably with 2,4-decadienyl and 2,4-undecadienyl derivatives. An additional appeal of this class of compounds is their close structural relationship to odoriferous substances. For example, the isovalerate of (2*E*,4Z)-2,4-decadien-1-ol (**43**, R = $H_{11}C_5$) has been identified as an essential constituent of natural cypress oil, while the odor of the next higher homologue (**44**, R = $H_{13}C_6$) resembles the typical musk scent. The syntheses of both products was accomplished with over-all yield of 47% and 61%, respectively, by metalation of (Z)-1,4-decadiene or -undecadiene with *sec*-butyllithium, condensation with fluorodimethoxyborane followed by oxidation with alkaline hydrogen peroxide and, finally, esterification with isovaleryl chloride in the presence of pyridine [50].



43: R = $H_{11}C_5$
44: R = $H_{13}C_6$

The introduction of a pair of geminal methyl groups at a terminal position of the pentadienyl moiety reduces the choice of truely coplanar conformers to the *S* form, carrying the substituents at the handle of the sickle, and the *W* form. 5-Methyl-2,4-hexadienyllithium (**45**, M = Li) and -potassium (**45**, M = K) were generated by the metalation of 5-methyl-1,4-hexadiene with *sec*-butyllithium or with trimethylsilylmethylpotassium in tetrahydrofuran. The dimethoxyborylation/oxidation sequence afforded (*Z*)- and (*E*)-5-methyl-2,4-hexadien-1-ol with ratios of 1 : 4 and 2 : 3, respectively. Identical *cis/trans* ratios were obtained when the lithium and potassium derivatives were prepared by reductive cleavage of (*Z*)-5-methyl-2,4-pentadienyl phenyl ether with the biphenyl/lithium and biphenyl/potassium "radical anions" at 0 °C [51].

S-45

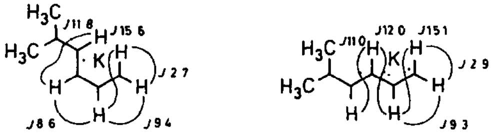


W-45

M = Li 1 4
M = K 2 3

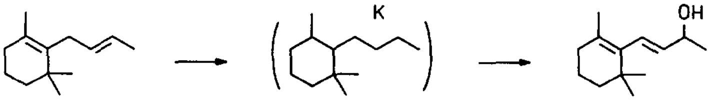
^{1}H-Nmr spectroscopy confirmed the structural assignments made on the basis of the trapping experiments. Vicinal coupling constants of 8.6 and 12.0 Hz were recorded for the hydrogen nuclei at C(2) and C(3) of the *S* form ($\delta_{H,C(3)}$ 3.31) and *W* form ($\delta_{H,C(3)}$ 3.96), respectively [51].

S-45



W-45

The structurally related (*E*)-2-(2-butenyl)-1,3,3-trimethylcyclohexene reacted only sluggishly with trimethylsilylmethylpotassium over 16 h at -50 °C. After interception with fluorodimethoxyboron and oxidation, β-ionol (30%) was isolated. The organometallic precursor (**46**) must have had the *W* conformation [51].



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Investigation of 4,5-didehydro-2,4-pentadienylmetal intermediates **47** has not always given conclusive answers. The main problem with such species is their propensity to react with electrophiles preferentially at the 3- or 5-position. For example, (*E*)-1-ethoxy-4-decen-1-yne gave ethyl (4*E*)-2,4-decadienoate (77%, about 1 : 1 *cis/trans* at the α,β-double bond) after being consecutively treated with *sec*-butyllithium, fluorodimethoxyboron and alkaline hydrogen peroxide [52]. 5-Trimethylsilyl-4,5-didehydro-2,4-pentadienyllithium (**47**, M = Li) or -potassium (**47**, M = K) reacted with methyl iodide and aliphatic aldehydes exclusively at the 3-position. In other words, all stereochemical information was lost. The hook-like *endo* configuration of the species **47** was, however, established by the borylation/oxidation sequence which produced pure (*Z*)-5-trimethylsilyl-2-penten-4-yn-1-ol [52]. 3,5-Bis(trimethylsilyl)-4,5-didehydro-2,4-pentadienylmetals (**48**, R = H_3C) and 3-triethylsilyl-5-trimethylsilyl-4,5-

didehydro-2,4-pentadienylmetals (**48**, R = H_5C_2) reacts with all sorts of electrophiles preferentially or exclusively at the unsubstituted terminal position. The *(Z)* configuration of the resulting products argues again for an *endo* shaped precursor [52].

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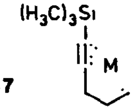

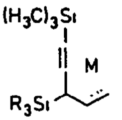

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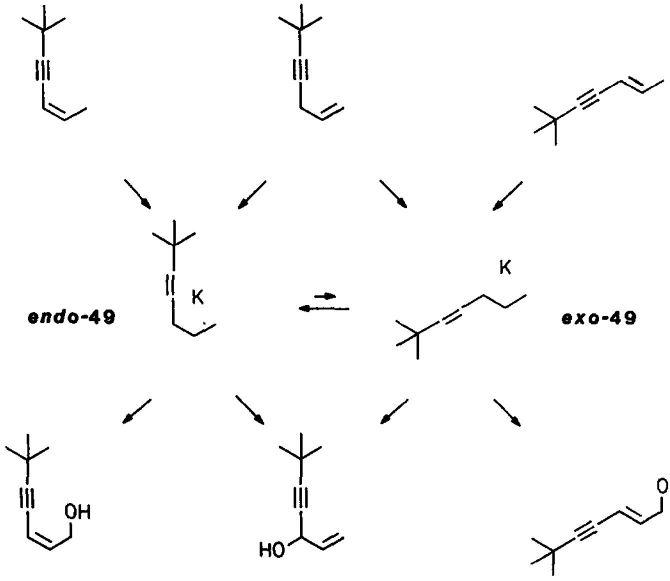
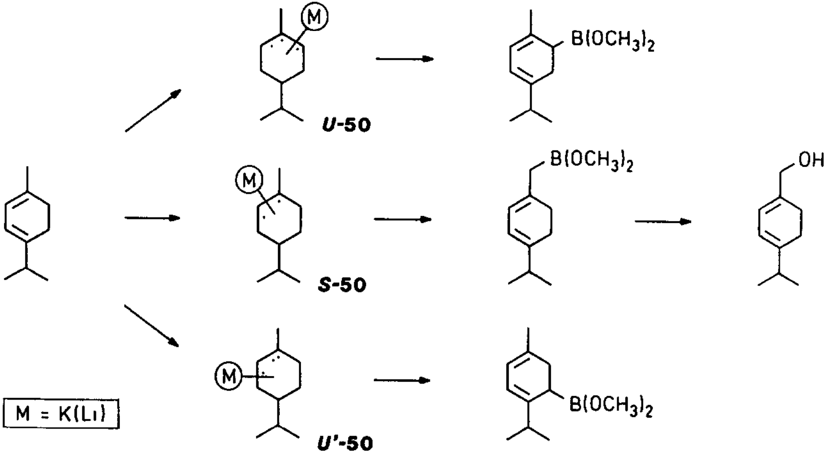
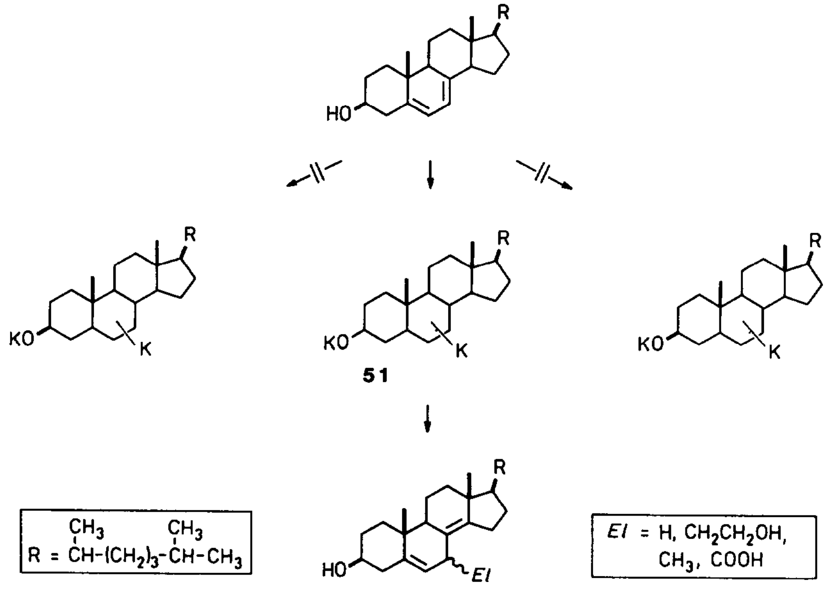
The carba-analogous 6,6-dimethyl-4,5-didehydro-2,4-heptadienyl-potassium **49** [52] was generated from pure stereoisomers or *(Z/E)* mixtures of 6,6-dimethyl-2-hepten-4-yne by exposure to trimethylsilylmethylpotassium in hexane during 24 h at 25 °C. Methyl iodide was found to attack this species again almost exclusively at the 3-position. The borylation/oxidation sequence, however, afforded *(Z)*- and *(E)*-6,6-dimethyl-2-hepten-4-yn-1-ol (55%) in the ratio 98 : 2 as well as 6,6-dimethyl-1-hepten-4-yn-3-ol (23%). When tetrahydrofuran was used as the solvent, the *endo* preference was attenuated to some extent. The primary alcohols were then formed with *(Z/E)* ratios of not more than 91 : 9.



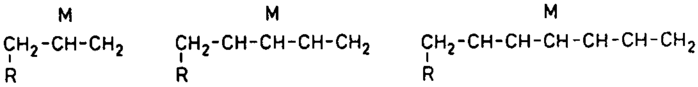
So far, all of the organometallics studied had acyclic (or, in the case of **46**, exocylic) allyl and pentadienyl backbones. Hence they were subject to torsional isomerization. Rigid substrates can also provide valuable insight into the structural preferences of resonance stabilized organometallic compounds. This is particularly the case if deprotonation can occur at different sites, generating each time another "frozen conformer". α-Terpinene is such a hydrocarbon having four non-equivalent allyl positions. According to our rule of thumb (see Chapter 3.1), metalating reagents should attack the allylic methyl group much more rapidly than any of the methylene groups. This would lead to a pentadienylmetal species (***S*-50**) having an *S* shaped area of delocalization. As we have seen, such a geometry is not very favorable. Potassium derivatives, at least, prefer *U* shapes. Therefore, when α-terpinene was treated with the LICKOR base in tetrahydrofuran at -45 °C three organometallic isomers (***U*-50**, ***S*-50** and ***U'*-50**) were formed concomitantly, the methine site being inert. Fortunately, the system is selfadjusting. After addition of fluorodimethoxyboron, a mixture composed of three boronates was obtained in roughly equal amounts. Upon oxidation with alkaline hydrogen peroxide one single alcohol (4-isopropyl-1,3-cyclohexadienylmethanol, "anthemol", 44%), was isolated. This was the regioisomer derived from the exocyclic intermediate. The two endocyclic isomers underwent spontaneous elimination to give 1-isopropyl-4-methylbenzene (*p*-cymene, 50%) [53].



7,8-Dehydrocholesterol (pro-vitamin D_3) again contains three different allyl positions. However, access to two of them is blocked by severe steric hindrance. The methylene group at the 4-position suffers from the closeness of the angular methyl group and, even worse, of the hydroxy function which, after deprotonation by the metalating reagent, forms a bulky alcoholate cluster, while the methine center at the 9-position is surrounded by three coaxial hydrogen atoms. Thus, only the methine hydrogen at position 14 can be successfully abstracted, giving rise to a *S* shaped pentadienyl metal intermediate **51** which undergoes electrophilic substitution exclusively at the 7-position (43%, if *El* = COOH) [54].



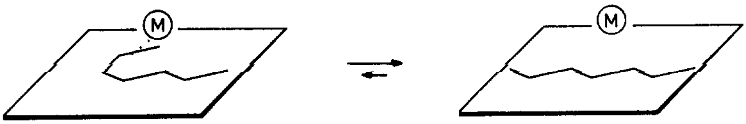
The number of coplanar, hence resonance stabilized, structures increases considerably when an allyl is extended to a pentadienyl moiety : three possible conformers rather than a single one for the parent systems, eight rather than two if a substituent is attached to one of the termini. The manifolds proliferate to 10 and 32, respectively, when an additional olefinic entity is attached to the pentadienyl moiety to give a heptatrienyl species.



$\underset{R}{CH_2}-\overset{M}{CH}-CH_2$ $\quad$ $\underset{R}{CH_2}-CH-\overset{M}{CH}-CH-CH_2$ $\quad$ $\underset{R}{CH_2}-CH-CH-\overset{M}{CH}-CH-CH-CH_2$

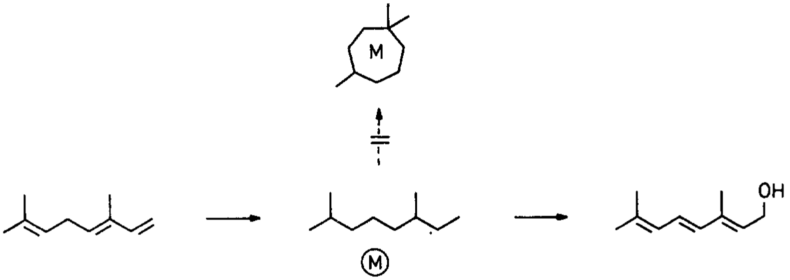
R = H	1	3	10
R = Alkyl	2	8	32

It may appear futile to continue to strive for stereoselectivity under such circumstances. On the other hand, as we have already seen, organometallic compounds have a pronounced partiality for special geometries. Therefore, a discrimination between the various options may occur even when the choice becomes embarrassingly large. This has been found to be true. The ^1H- and ^{13}C-nmr spectra of 2,4,6-heptatrienylpotassium reveal the presence of just two conformers which coexist in the ratio of 15 : 85. The major conformer has without doubt the perfect zigzag band form (*W*-*W*-**52**). The minor component probably contains a serpent-like backbone domain between carbons 2 and 6 to which either two *exo* or one *exo* and one *endo* oriented methylene groups are attached. Presently we favor the second hypothesis and tentatively assign to it the structure of a *U*-*W* composite (*U*-*W*-**52**) [55].



U-*W*-**52** *W*-*W*-**52**

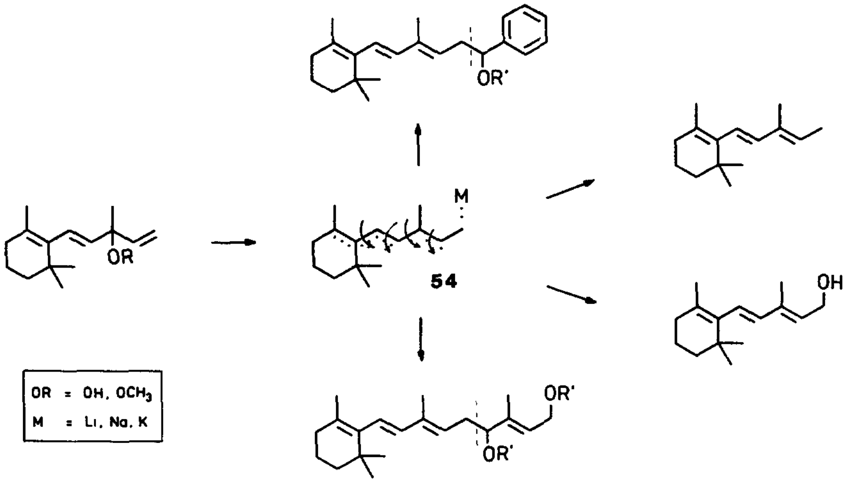
Branching methyl groups at the electron-rich centers tend to occupy the *endo* position and thus favor the *W* alignment of the delocalized backbone, as we have already seen in the pentadienyl series. The *endo* preference manifests itself also in the heptatrienyl series. Organo-lithium or -potassium promoted metalation of β-ocimene (3,7-dimethyl-1,3,6-octatriene) generates an organometallic intermediate **53** [56], the electrocyclic ring closure [57] of which can be prevented at low temperatures. Hydroxylation *via* the boronate intermediate affords (2*E*,4*E*)-4,5-didehydrogeraniol (68%) containing virtually no trace of stereoisomeric contamination [56].



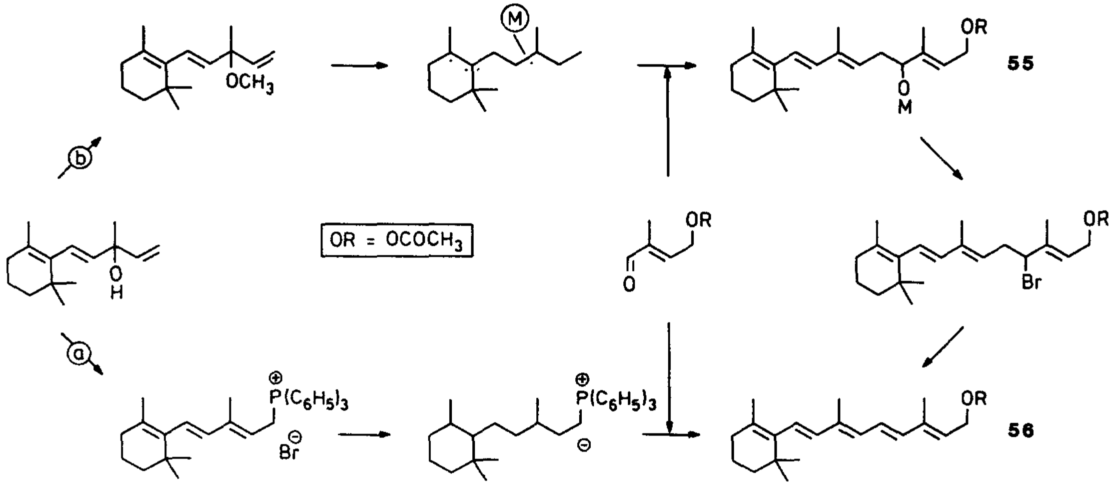
Ocimene **53** *Dehydro-geraniol*

M = Li or K

By bridging positions 6 and 8 of ocimene to form a six-membered ring and adding a pair of *gem*-methyl groups, the monoterpene is elaborated into a sesquiterpenoid. The organometallic C_{15} building block **54** is more conveniently prepared by reductive cleavage of the methyl vinyl-β-ionol ether with lithium metal or potassium/sodium alloy rather than by metalation of a suitable triene precursor. Intermediate **54** has four degrees of rotational freedom. At the moment of its generation more than a dozen different conformers may emerge simultaneously. However, it takes only a very short while for torsional equilibration to restore stereochemical order. The perfect *all-trans* configuration of products obtained after protonolysis (78% of 2-[(1*E*,3*E*)-3-methyl-1,3-pentadienyl]-1,3,3-trimethylcyclohexene), boronate mediated hydroxylation (75% of (2*E*,4*E*)-5-(2,6,6-trimethyl-1-cyclohexenyl)-3-methyl-2,4-pentadien-1-ol) or nucleophilic addition to an aldehyde is convincing evidence for the *W-W* shape of the delocalized backbone in **54** [56].



The adduct formed upon combination of intermediate **54** with (*E*)-4-acetoxy-2-methyl-2-butenal ("3-formyl-*cis*-crotyl acetate") was isolated after neutralization (**55**, OM = OH) or acetylation (**56**, OM = $OCOCH_3$) with 28 - 65% yield, depending on the exact working protocol. Simple dehydration of the secondary alcohol (**55**, OM = OH) should, in principle, lead directly to the desired vitamin A acetate (**56**).



Unfortunately, we were unable to eliminate water under sufficiently mild conditions and it was necessary to resort to a replacement of the hydroxy group by bromine using phosphorus tribromide in the presence of pyridine. Dehydrobromination was then smoothly accomplished with 1,8-diazabicyclo[5.4.0]undec-7-ene ("DBU"). After short exposure to light in the presence of trace amounts of elementary iodide, analytically pure *all-trans*-vitamin-A acetate (**56**, OR = $OCOCH_3$, 15% over-all) was isolated chromatographically [58].

A comparison of this novel, organometal mediated vitamin-A synthesis with the well-known technical process of the BASF [59] is quite instructive. In both cases, vinyl-β-ionol and 4-acetoxy-2-methyl-2-butenal are used as the C_{15} and C_5 units. The industrial method (Route a) implied the conversion of the alcohol first into a phosphonium salt, which is contaminated by the (13Z) isomer and must be purified by fractional crystallization. Treatment with a base then generates the nucleophilic phosphorus ylid, which upon addition of the aldehyde, undergoes a Wittig reaction to give the perconjugated polyene chain in a straightforward manner. As we have already seen, the construction of the Δ^{11}-double bond by our method (Route b) is more cumbersome. Nevertheless, the organometallic approach offers two significant advantages. First, it involves a truly "autostereoselective" step : intermediate **54** adopts the *W-W* shape *spontaneously*. Attachment of an electrophile at the terminal position of the chain must inevitably impose the *(E)*-configuration on the resulting Δ^9-double bond. This is crucial, since controlled *(Z)* → *(E)* isomerizations at three-fold substituted olefinic bonds of polyenes can only be accomplished with difficulty, if at all. The second asset of the organometallic approach is of ecological importance. Since no triphenylphosphine is employed, there is no need either to recycle or to dispose of the triphenylphosphine oxide, a major problem of all Wittig reactions.

4. ABOUT THE ORIGIN OF THE "*endo* EFFECT"

The strange *endo* preference of allyl type potassium (and cesium) compounds was discovered in 1974. Since then this structural preference has been recognized to be widespread and of great practical importance. The latter aspect has received much attention. We have made use of the mysterious *endo* effect to propose novel methods for stereocontrolled organic synthesis, in particular, carbon-carbon bond forming reactions. The origin of the *endo* preference, however, is still obscure.

Before we go into detail, we must repeat a warning. The message is trivial but it is still sometimes forgotten as one must conclude from views expressed in literature. When we address the problem of the *endo* preference, we deal with equilibrium compositions, and hence ground state energies. If we wish to understand why the base catalyzed isomerization of 1-alkenes gives 2-alkenes with high *cis/trans* ratios [60] we have to discuss relative rates and transition states. On one side *thermodynamic*, on the other *kinetic* quantities. Precise differentiation between is essential. Although they may parallel each other, there is no reason why they should. Actually, at least in one case, opposite stereopreferences have been observed depending on whether deprotonation is accomplished reversibly or irreversibly. When treated with trimethylsilylmethylpotassium in tetrahydrofuran at -75 °C, *cis*-4,4-dimethyl-2-pentene undergoes hydrogen/metal exchange 15 times faster than the *trans* isomer, despite the substantially greater thermodynamic stability ($\Delta G°$ 1.0 - 1.5 kcal/mol) of the *trans* derived *exo* over the *cis* derived *endo* form of the allylpotassium intermediate in this special case [61].

4.1 Previous Hypotheses

Possible reasons for the *endo* preference of all straight-chain or singly branched 2-alkenylpotassium species have been extensively discussed in previous articles [17, 24]. Hydrogen bonding of a δ- or ε-alkyl group across the half-circle of the *endo* species to the electron-rich unsubstituted allyl terminus (**57** and **58**, respectively; metal omitted for clarity) became the favorite explanation for quite a while.

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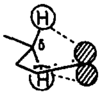

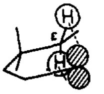

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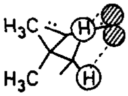
If this kind of extra stabilization were to be proven, would this not immediately imply that the *cis*-butenyl anion had a lower proton affinity than the allyl anion itself ? Not necessarily so. Although one may argue about the accuracy of the numbers, we can make the plausible assumption that, relative to allyl, the *cis*- and *trans*-2-butenyl anions are 2 and 5 kcal/mol more basic, respectively. Alkyl substituents always tend to destabilize adjacent carbanions. It is difficult to evaluate accurately to what extent this happens in any given case. The problem is, then, to know which number (*e.g.*, 2 or 5 kcal/mol) has to be considered as "normal" and which is the exception.

It occurred to us that a *tert*-butyl group placed at the 2-position should be also capable of establishing hydrogen bridges towards the allyl terminus (**59**, metal again omitted). Possibly it would even exert a much stronger stabilizing interaction since its adverse (destabilizing) electronic effect should not be transmitted through the nodal point.



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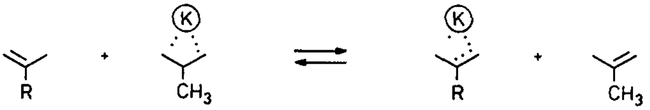
Therefore, we undertook a systematic study in order to quantify the effect which alkyl substituents have on the thermodynamic stability of allylmetal species. A series of 2-alkylallylpotassium compounds **60** was dissolved in tetrahydrofuran and the acid-base equilibrium with isobutene by counter-current hydrogen and metal transfer was allowed to become established. At -25 °C, it took several hours before the exchange was complete. The corresponding lithium derivatives were virtually unreactive even at ambient temperature. In control experiments, the equilibrium positions were also approached from the other side, *i.e.* using 2-methyl-1-alkenes and 2-methylallylpotassium as the starting components [62].



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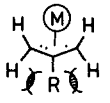
The results leave no doubt about the role of alkyl groups attached to the 2-position. All of them, including the *tert*-butyl group, destabilize the allylmetal species : methyl, ethyl or isopropyl by approximately 2.0, *tert*-butyl by 3.5 kcal/mol (see Table 3) [62].

Table 3. Relative thermodynamic stabilities $\Delta G°$ of 2-alkylallylpotassium species (**60**) and equilibrium constants K derived from transmetalation reactions involving allylpotassium, 2-methyl-, 2-ethyl-, 2-isopropyl- and 2-*tert*-butylallylpotassium as bases and the corresponding alkenes as acids (in tetrahydrofuran at -25 °C) [62].

Cpd. **60**	ΔpK_{248}	$\Delta G°_{248}$ [kcal/mol]
R = H	0.00	0.0
R = CH_3	1.60	1.8
R = CH_2CH_3	1.84	2.1
R = $CH(CH_3)_2$	2.15	2.4
R = $C(CH_3)_3$	3.10	3.5

It is tempting to rationalize these findings as being connected with the well-known widening of the central CCC angle of allyl anions and their metal derivatives, typically to 130°. Thus, the alkyl substituent R at the 2-position gets somewhat "squeezed in" between the two terminal *exo*-hydrogen atoms, the CCR angle being reduced to only 115° (see structure **61**). Steric repulsion certainly does play a role. However, if it were the sole or at least dominant factor, a methyl group should exert only a moderate, but a *tert*-butyl group an enormously detrimental effect. In reality, the introduction of a methyl group is penalized by 1.8 kcal/mol and its replacement by a *tert*-butyl group causes just an additional deterioration of similar magnitude only (1.7 kcal/mol) [62].



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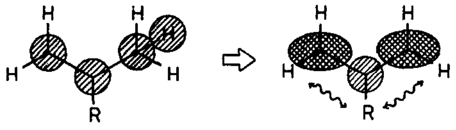
One may object that the observed destabilization by the *tert*-butyl group could be a net effect : strong steric repulsion partially compensated by hydrogen bonding to the electron-rich allyl termini. This kind of reasoning, however, ignores the data obtained with the isopropyl substituted species. In that case the essential benefits of hydrogen bonding could be retained at much reduced expense of steric strain. Nevertheless, the over-all effect of this alkyl group is also destabilizing.

4.2 A New Concept and its Generalization

An entirely new explanation appears to be required. It can be based on first-order electrostatic principles. Upon deprotonation of propene or a symmetrically substituted derivative thereof, the average charge density at the allyl termini increases by 0.5 electrons. The orbitals will have to expand (see top view **62**). For obvious reasons, most of the electron excess will accumulate at the outer periphery of the allyl moiety. A fraction thereof, however, will also find its way into the interior where it will inevitably affect the substituent at the 2-position. The bond that links the group R to the central carbon atom therefore lengthens in order to avoid extra electrostatic repulsion. Elongation means loss in binding energy and hence loss in thermodynamic stability.



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The increase in charge density should also manifest itself in an elongation of the *endo* and even more of the *exo* bonds. Conspicuously long bond distances have indeed been reported for methyl groups attached to polar allylmetal species [63].

5. CONCLUSIONS

In summary, we are presently inclined to understand the "*endo* preference" as a choice of the lesser of two evils. A substituent at the inside of the allyl half-moon is destabilizing but less so than if placed at the outside [64]. Whatever the correct rationale, the effect is of practical importance since it can be exploited in stereocontrolled syntheses as outlined above. Moreover, it appears to be just a special reflection of a more general phenomenon. Not only do isoelectronic species such as deprotonated Schiff bases or enolates show the same *endo* preference, but also metal-free analogues such as enamines, enethers, 1-halo-1-alkenes and 1,2-dihaloethylenes.

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64 Conclusions presented for the first time in the framework of a West Coast Lectureship in October 1990 at the chemistry departments of Vancouver, Pullman, Eugene, Corvallis, Palo Alto, Reno, La Jolla and Los Angeles.