

α -Deprotonated Allyl Ethers : Conformational Mobility and Conformational Preferences

Christian Margot, Paola Maccaroni, Frédéric Leroux and Manfred Schlosser *

Institut de Chimie organique de l'Université
Bâtiment de Chimie (BCh), CH-1015 Lausanne-Dorigny, Switzerland

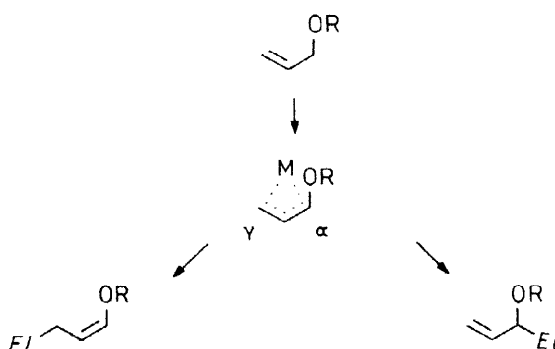
Received 22 June 1998; accepted 6 August 1998

Summary : *tert*-Butyllithium is best suited to accomplish a hydrogen/metal exchange at the α -position of γ -alkyl branched allyl ethers. Rapid torsional equilibration occurs at the γ -terminus of the deprotonated allyl unit while the alkoxy group at the α -site has to occupy the *exo* position in order to minimize steric repulsions. The introduction of an alkoxy group into the terminal position of a γ -branched 2-alkenyllithium lowers the barrier to torsional isomerization slightly (by a few kcal/mol).

© 1998 Elsevier Science Ltd. All rights reserved.

In 1942, Wittig and coworkers attempted the metalation of benzyl methyl ether and discovered the first anionic 1,2-migration of an oxygen attached alkyl group to the neighboring carbon atom ("Wittig rearrangement")¹. Although they could never characterize the postulated organometallic intermediate in this model case, five years later they were able to trap the structurally related 9-methoxy-9-fluorenyllithium with benzophenone².

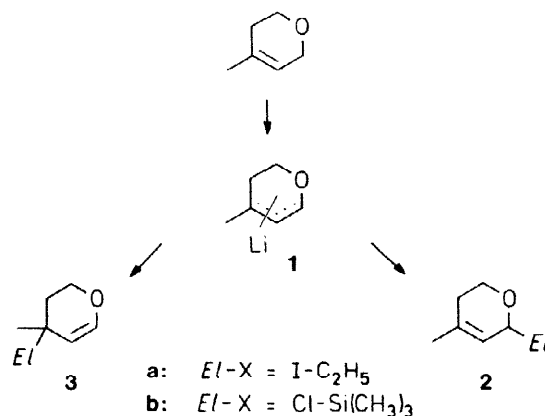
Despite close similarities, allyl ethers lagged behind benzyl ethers for a long time as far as the investigation of their organometallic derivatives is concerned. The first anionic isomerization of an allyl ether was reported in the fifties³. Eventually, in 1974, three groups independently described the successful interception of metalated allyl ethers by a variety of electrophiles⁴⁻⁶. The latter were found to attack the oxygen-adjacent α -position and the unsubstituted γ -position of the allyl unit concomitantly thus giving rise to mixture of regioisomers, the preponderant component being in most cases the enether or, after acid-catalyzed hydrolysis, the corresponding aldehyde. Later Hoppe *et al.* demonstrated that an almost perfect regiocontrol can be achieved in either sense, favoring α - or γ -substitution, by the proper choice of the metal⁷.



Neighboring alkyl substituents are known to diminish both the kinetic and thermodynamic acidity of alkenes^{8,9}. Using *N,N,N',N'*-tetramethylethylenediamine ("TMEDA") activated butyllithium, Rautenstrauch *et al.* were able to metalate 3,6-dihydro-2*H*-pyran¹⁰ and 2-methylallyl vinyl ether¹¹, but failed to deprotonate cyclogeranyl vinyl ether¹¹ at an allylic position. Hence the question arose whether the generation of γ -alkyl branched α -alkoxyallyllithium species would be possible at all.

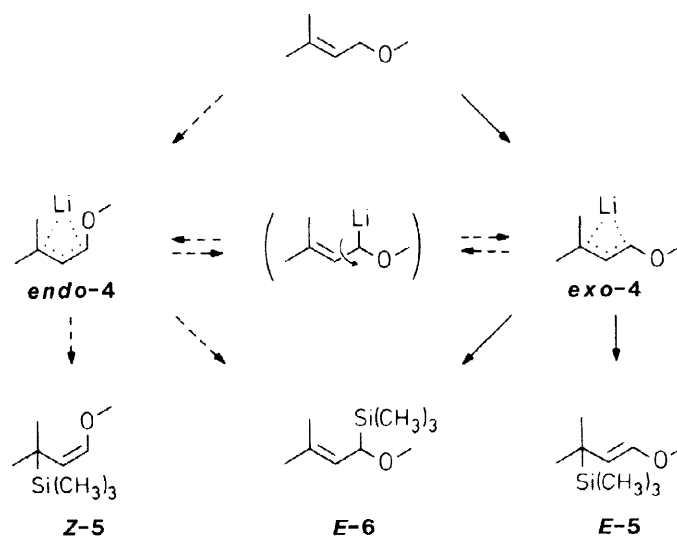
Fax ++41 / 21 / 692 39 65

For simplicity we selected 4-methyl-3,6-2*H*-pyran as the first substrate to be studied. Butyllithium, even in the presence of TMEDA, proved to be not reactive enough, only poor yields (20 - 30%) being obtained. However, using *tert*-butyllithium or TMEDA-activated *sec*-butyllithium allowed us to generate the intermediate **1** efficiently and to isolate, after reaction with ethyl iodide or chlorotrimethylsilane, the regioisomeric derivatives **2** and **3** in satisfactory total yields (45% - 60%).



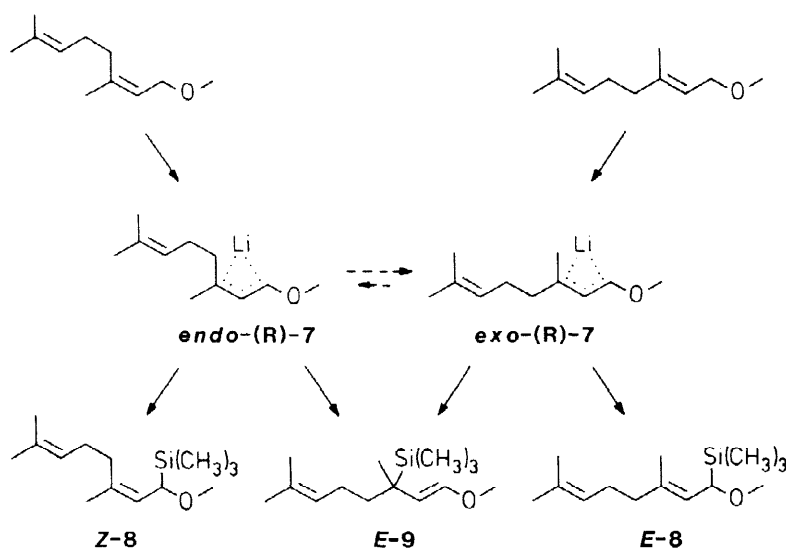
Having established a suitable metalation procedure, we now were able to turn to *acyclic* γ -alkyl branched α -methoxyallyllithium intermediates in order to address the inherent conformational problems. Previously an investigation of the lithiated crotyl 2-tetrahydropyranyl ether had revealed that a methyl group, when in competition with an alkoxy substituent, has to leave the electronically more favorable *endo* position to the latter and to content itself with the *exo* position¹². What will happen if a second alkyl group is introduced into the γ -position and one of them inevitably occupies an *endo* position at the inner allyl terminus? Should the steric congestion thus produced not oblige the alkoxy substituent to abandon the *endo* site and move to the *exo* site? This conclusion was found to be correct.

Methyl 3-methyl-2-butenyl ("prenyl") ether was metalated and treated with chlorotrimethylsilane. Only two products were identified in the reaction mixture, (1-methoxy-3-methyl-2-butenyl)trimethylsilane (*E*-6, 48%) and (*E*)-(3-methoxy-1,1-dimethyl-2-propenyl)trimethylsilane (*E*-5, 30%). The absence of the other stereoisomer (*Z*-5) rules out the intermediacy of the organometallic *endo* conformer (*endo*-4) in any substantial amount and confirms the prediction of a largely preponderant *exo* conformer (*exo*-4).



Independent evidence for the *exo*-conformation was sought by nmr spectroscopy. Unfortunately, it was not possible to observe the H^{α},H^{β} -coupling constant because of extensive broadening of all signals. On the other hand, the geminal methyl groups remained non-equivalent over the entire accessible temperature range between -100 and -25 °C. The barrier to rotation around the C^{β},C^{γ} -axis must consequently exceed 10 kcal/mol, as one would expect.

If the conformational mobility cannot be detected on the nmr-spectroscopic time scale, the torsional equilibration can be followed by monitoring the isomeric composition of γ,γ -dialkyl substituted α -alkoxyallylic species at low temperatures as a function of time. When methyl neryl ether and geranyl methyl ether were separately metalated with *tert*-butyllithium in tetrahydrofuran (THF) or diethyl ether (DEE) at -75 °C and the organometallic intermediates were trapped after 6 h with chlorotrimethylsilane, virtually the same product mixture composed of the (*Z*)-allyl ether *Z*-8, the *trans*-enether *E*-9 and the (*E*)-allyl ether *E*-8 was obtained (see Table). In contrast to this stereoconvergence observed at -75 °C, the original configuration was retained to a large extent when the metalation was carried out in the course of 2 h at -100 °C (in THF or DEE) or at -125 °C (in a 1 : 1 mixture of THF and pentanes). In other words, the torsional interconversion of the stereoisomeric intermediates carrying the alkyl chain ["R"] in the *endo*- or *exo*-position, *endo*-[R]-7 and *exo*-[R]-7, occurs only slowly at such low temperature.



The temperature dependence of the *endo/exo*-stereomutation rate suggests an activation energy in the vicinity of 14 kcal/mol for this process. We assume the C(2),C(3)-rotational barrier of prenyllithium (3-methyl-2-butenyllithium) to approximate 17 kcal/mol, this estimate being based on the knowledge of the torsional activation energies of prenylmagnesium bromide (at the inner allylic bond, 7 kcal/mol ?)¹³, allylmagnesium bromide (< 7 kcal/mol)¹⁴, allyllithium (11 kcal/mol)¹⁵, allylpotassium (17 kcal/mol)¹⁶ and prenylpotassium (\geq 22 kcal/mol)¹⁷. Evidently, the introduction of a methoxy group into the terminal position of prenyllithium lowers the torsional barrier by some 3 (\pm 2) kcal/mol relative to the parent compound. This difference can be attributed to two factors which may operate simultaneously : destabilization of the allyllithium species by an electron-repulsive interaction¹⁸ with the *exo*-positioned alkoxy group and, at least partial, restoration of the typical enether resonance¹⁹ between the double bond and the non-bonding electrons of the oxygen at the transition state of the rotation, when the C,Li-bond and the olefinic π -orbitals are orthogonally oriented.

Table. Metalation of methyl neryl ether and geranyl methyl ether with *tert*-butyllithium (1.0 molar equiv.; 0.75 M concentrations) in various solvents at -75 °C, -100 °C or -125 °C followed by trapping with chlorotrimethylsilane : combined yields of products [8 + 9], regioisomeric ratios [8/(8 + 9) \equiv $\alpha/(\alpha + \gamma)$] and stereoisomeric ratios [Z-8/E-8].

solvent ^{a)}	conditions	neryl series ^{b)}			geranyl series ^{b)}		
		yield	$\alpha/(\alpha+\gamma)$	Z-8 : E-8	yield	$\alpha/(\alpha+\gamma)$	Z-8 : E-8
THF	6 h - 75 °C	79%	0.54	21 : 79	77%	0.53	19 : 81
THF	6 h -100 °C	45%	0.40	79 : 21	-	-	-
THF	2 h -100 °C	32%	0.45	94 : 6	45%	0.46	8 : 92
DEE	6 h - 75 °C	62%	0.85	20 : 80	66%	0.78	21 : 79
DEE	6 h -100 °C	59%	0.76	39 : 61	-	-	-
DEE	2 h -100 °C	17%	0.73	91 : 1	30%	0.33	7 : 93
THF/PEN	2 h -125 °C	46%	0.56	84 : 16	40%	0.61	2 : 98
DEE/PEN	2 h -125 °C	37%	0.61	21 : 79	47%	0.23	4 : 96
PEN	2 h -125 °C	36%	0.45	18 : 82	26%	0.22	6 : 94

a) THF = tetrahydrofuran; DEE = diethyl ether; PEN = pentanes; THF/PEN and DEE/PEN as 1 : 1 (v/v) mixtures.

b) Neryl and, respectively, geranyl methyl ether as the starting material.

EXPERIMENTAL PART

1. Generalities

¹H-nmr spectra were recorded at 400 MHz, the samples being dissolved in deuteriochloroform. For standard working practice and abbreviations, see recent articles²⁰ from this laboratory.

2. Metalation of Allyl Type Ethers and Subsequent Electrophilic Substitution

a) *4-Methyl-3,6-dihydro-2H-pyran*²¹ as the substrate : A precooled (-90 °C) solution of the cyclic ether (10 g, 0.10 mol) and *N,N,N',N'*-tetramethylethylenediamine (15 mL, 12 g, 0.10 mol) in tetrahydrofuran (0.10 L) was added to *sec*-butyllithium (0.10 mol) from which the solvent had been stripped off under reduced pressure. After 5 h at -75 °C, ethyl iodide (8.9 mL, 17 g, 0.11 mol) was introduced. When the mixture had reached 25 °C, it was poured into water (0.25 L) and extracted with pentane (3 \times 30 mL). The combined organic layers were concentrated and the residue distilled at a bath temperature of 40 °C and at a pressure of 0.01 mmHg. A clear liquid was collected which contained 60% of the regioisomers **2a** and **3a** in the ratio of 2 : 1. - Analysis : calc. for C₈H₁₄O (126.20) C 76.14, H 11.18, found C 75.77, H 10.98%. - The isomers were separated by preparative gas chromatography (3 m, 10% SE-30, 70 \rightarrow 140 °C [5 °C/min]) : **4-Ethyl-4-methyl-3,4-dihydro-2H-pyran (2a)** : ¹H-NMR (C₆D₆) : δ 6.37 (1 H, d, *J* 6.4), 4.40 (1 H, d, *J* 6.4), 3.7 (2 H, m), 1.47 (1 H, ddd, *J* 13.8, 8.3, 4.2), 1.2 (3 H, m), 0.87 (3 H, s), 0.77 (3 H, t, *J* 7.5). - MS : 126 (20%, *M*⁺), 111 (7%), 97 (100%). - **2-Ethyl-4-methyl-5,6-dihydro-2H-pyran (3a)** : ¹H-NMR (C₆D₆) : δ 5.25 (1 H, s, broad), 3.9 (1 H, m), 3.87 (1 H, ddd, *J* 11.2, 5.9, 2.0), 3.45 (1 H, ddd, *J* 11.2, 10.3, 4.0), 2.0 (1 H, m), 1.56 (3 H, s), 1.5 (3 H, m), 1.00 (3 H, t, *J* 7.5). - MS : 126 (13%, *M*⁺), 111 (20%), 97 (100%).

In a similar reaction, 4-methyl-5,6-dihydro-2*H*-pyran (0.10 mol) was consecutively treated with *tert*-butyllithium (0.11 mol, 5 h at -75 °C in 0.10 L of tetrahydrofuran) and chlorotrimethylsilane (14 mL, 12 g, 0.11 mol). The sole product isolated by distillation and preparative gas chromatography (3 m, 10% SE-30, 80 °C → 160 °C) was 4-methyl-2-trimethylsilyl-5,6-dihydro-2*H*-pyran (**3b**); 43%. - ¹H-NMR (C₆D₆) : δ 5.42 (1 H, s), 3.95 (1 H, ddd, *J* 10.6, 5.9, 1.2), 3.9 (1 H, m), 3.40 (1 H, dt, *J* 10.7, 3.2), 2.15 (1 H, symm. m), 1.61 (3 H, s), 1.47 (1 H, dt, *J* 16.7, 2.9), 0.11 (9 H, s). - MS : 170 (1%, *M*⁺), 155 (35%), 97 (12%), 73 (100%). - It was found to be too labile to be sent abroad for elemental analysis.

b) *Methyl 3-methyl-2-butenyl ether*²² as the substrate : A precooled (-75 °C) solution of the prenyl ether (2.0 g, 20 mmol) in tetrahydrofuran (20 mL) was added to *tert*-butyllithium (20 mmol) from which the solvent had been stripped off under reduced pressure. After 4 h at -50 °C, chlorotrimethylsilane (2.8 mL, 2.4 g, 22 mmol) was added at -75 °C. The dark red reaction mixture decolorized instantaneously. A small sample was withdrawn and the product composition was determined by gas chromatography (5 m, 5% C-20M, 60 → 160 °C) relative to tetradecane as an internal standard : 8% of the starting material, 30% of *E*-5 and 48% of **6**. The reaction mixture was poured into water (0.10 L) and extracted with hexanes (2 × 25 mL). The organic material was concentrated and distilled. A first fraction (bp 60 - 65 °C/20 mmHg) contained mainly the enether *E*-5 and the third fraction (90 - 95 °C/20 mmHg) mainly the allyl ether **6**. The products were purified by preparative gas chromatography (2 m, 5% SE-30, 75 °C → 150 °C). - (*E*)-(3-Methoxy-1,1-dimethyl-2-propenyl)trimethylsilane (*E*-5) : 30%; bp 145 - 147 °C; n_D²⁰ 1.4349. - ¹H-NMR (CDCl₃) : δ 6.11 (1 H, d, *J* 12.7), 4.83 (1 H, d, *J* 12.7), 3.50 (3 H, s), 0.97 (6 H, s), -0.04 (9 H, s). - Analysis : calc. for C₉H₂₀OSi (172.34) C 62.72, H 11.70; found C 63.01, H 11.73%. - (1-Methoxy-3-methyl-2-butenyl)trimethylsilane (**6**) : 48%; mp -25 to -23 °C; bp 153 - 155 °C; n_D²⁰ 1.4420. - ¹H-NMR (CDCl₃) : δ 5.13 (1 H, dm, *J* 10.3), 3.65 (1 H, d, *J* 10.3), 3.25 (3 H, s), 1.77 (3 H, s), 1.62 (3 H, s), 0.01 (9 H, s). - Analysis : calc. for C₉H₂₀OSi (172.34) C 62.72, H 11.70; found C 62.88, H 12.03%.

c) *Methyl neryl ether*²³ and *geranyl methyl ether*²³ as substrates : A solution of the neryl or geranyl ether (4.2 g, 25 mmol), butyllithium (25 mmol) and *N,N,N',N'',N'''*-pentamethyldiethylenetriamine (4.3 g, 25 mmol) in tetrahydrofuran (25 mL) was kept 2 h at -75 °C. Addition of chlorotrimethylsilane (3.3 mL, 2.8 g, 26 mmol) caused a rapid decoloration of the dark red reaction mixture. The latter was poured into water (0.10 L) and extracted with hexanes (2 × 25 mL). The product composition in an aliquot was analyzed by gas chromatography (3 m, 5% SE-30, 80 → 180 °C; 30 m, DB-1701, 75 → 180 °C; nonane as an internal standard) : 9% of the allyl ether *Z*-8, 42% of the allyl ether *E*-8 and 27% of the enether *E*-9. The solvent was evaporated and the residue submitted to a short-path distillation using a Hickmann flask, bp 60 - 85 °C/0.1 mmHg. - Analysis : calc. for C₁₄H₂₈OSi (240.46) C 69.93, H 11.74; found C 69.82, H 11.83%. - The two regioisomers were separated by preparative gas chromatography : (*Z*)- and (*E*)-(1-Methoxy-3,7-dimethyl-2,6-octadienyl)trimethylsilane (*Z*- and *E*-8 in the ratio of 15 : 85) : ¹H-NMR (CDCl₃) : δ 5.15 (1 H, d, *J* 10.4), 5.10 (1 H, t, *J* 6.3), 3.69 (1 H, d, *J* 10.4), 3.26 (3 H, s), 2.1 (4 H, m), 1.80 (0.15 × 3 H, s), 1.70 (0.85 × 3 H, s), 1.61 (6 H, s), 0.02 (9 H, s). - [1-(2-*trans*-Methoxyethenyl)-1,5-dimethyl-4-hexenyl]trimethylsilane (*E*-9) : ¹H-NMR (CDCl₃) : δ 5.97 (1 H, d, *J* 12.9), 5.13 (1 H, *thept*, *J* 7.1, 1.4), 4.77 (1 H, d, *J* 12.9), 3.53 (3 H, s), 1.94 (2 H, q, *J* 7.0), 1.71 (3 H, d, *J* 1.3), 1.62 (3 H, s), 1.4 (2 H, m), 0.99 (3 H, s), -0.01 (9 H, s).

Further reactions were performed varying the solvent, the reagent and the temperature as specified in the Table. The products were identified and quantified by gas chromatography (as described above).

3. Temperature Dependent NMR Studies

All manipulations were carried out in a nitrogen atmosphere. A solution of *tert*-butyllithium (0.50 mmol) in pentanes (0.35 mL) was transferred by means of a nitrogen purged pipette into a 5 mm wide nmr tube attached to a two-neck adapter. The solvent was stripped off, the tube was immersed in a dry ice/acetone bath and precooled perdeuterated THF (0.50 mL) and 1-methoxy-3-methyl-2-butene (0.040 g, 0.40 mmol) were added using a nitrogen purged syringe. After being cooled with liquid nitrogen, the tube was sealed under vacuum. The mixture was kept 6 h at -50 °C, before ¹H-nmr spectra were recorded at 400 MHz, the signal of residual hydrogen at the 2-position of the solvent (δ 3.58) serving as an internal shift reference. The temperature was varied between -100 °C and -25 °C and determined by the methanol probe method.²⁴ Temperature-dependent spectral changes proved to be reproducible upon repetition of the cold-warm-cold cycle, but all in all were minor and uncharacteristic.

Acknowledgment : This work was financially supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Bern (grants 20-446-084, 20-25'577-88 and 20-49'307-96) and the Fondation Herbette, Lausanne.

REFERENCES

1. Wittig, G.; Löhmann, L.; *Liebigs Ann. Chem.* **1942**, *550*, 260 - 268.
2. Wittig, G.; Happe, W.; *Liebigs Ann. Chem.* **1947**, *557*, 205 - 220.
3. Hauser, C.R.; Kantor, S.W.; *J. Am. Chem. Soc.* **1951**, *73*, 1437 - 1441; for other sporadic examples see : Schlosser, M.; *J. Organomet. Chem.* **1967**, *8*, 9 - 16 [first footnote]; Felkin, H.; Tambuté, A.; *Tetrahedron Lett.* **1969**, *10*, 821 - 822; Rautenstrauch, V.; *J. Chem. Soc., Chem. Commun.* **1970**, 4 - 6.
4. Evans, D.A.; Andrews, G.C.; Buckwalter, B.; *J. Am. Chem. Soc.* **1974**, *96*, 5560 - 5561; Evans, D.A.; Baillargeon, D.J.; Nelson, J.V.; *J. Am. Chem. Soc.* **1978**, *100*, 2242 - 2244.
5. Still, W.C.; Macdonald, T.L.; *J. Am. Chem. Soc.* **1974**, *96*, 5561 - 5563; *J. Org. Chem.* **1976**, *41*, 3620 - 3622.
6. Hartmann, J.; Muthukrishnan, R.; Schlosser, M.; *Helv. Chim. Acta* **1974**, *57*, 2261 - 2275; Hartmann, J.; Stähle, M.; Schlosser, M.; *Synthesis* **1974**, 888 - 889; Schlosser, M.; Strunk, S.; *Tetrahedron* **1989**, *45*, 2649 - 2664.
7. Hoppe, D.; Hanko, R.; Brönneke, A.; *Angew. Chem.* **1980**, *92*, 637 - 639; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 625 - 627; Hoppe, D.; *Angew. Chem.* **1984**, *96*, 930 - 946; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 932 - 948.
8. Schlosser, M.; *Pure Appl. Chem.* **1988**, *60*, 1627 - 1634.
9. Schlosser, M.; in *Organometallics in Synthesis : A Manual* (ed. : Schlosser, M.), Wiley, Chichester, **1994**, Chapter 1.
10. Rautenstrauch, V.; *Helv. Chim. Acta* **1972**, *55*, 594 - 609; corr. 3064 - 3066.
11. Rautenstrauch, V.; Büchi, G.; Wüest, H.; *J. Am. Chem. Soc.* **1974**, *96*, 2576 - 2580.
12. Moret, E.; Schlosser, M.; *Tetrahedron Lett.* **1984**, *25*, 4491 - 4494.
13. Whitesides, G.M.; Nordlander, J.E.; Roberts, J.D.; *J. Am. Chem. Soc.* **1962**, *84*, 2010 - 2011.
14. Nordlander, J.E.; Roberts, J.D.; *J. Am. Chem. Soc.* **1959**, *81*, 1769 - 1770.
15. West, P.; Purmort, J.I.; McKinley, S.V.; *J. Am. Chem. Soc.* **1968**, *90*, 797 - 798; Zieger, H.E.; Roberts, J.D.; *J. Org. Chem.* **1969**, *34*, 1976 - 1977.
16. Thompson, T.B.; Ford, W.T.; *J. Am. Chem. Soc.* **1979**, *101*, 5459 - 5464.
17. By analogy with the rate found for the *endo/exo*-isomerization of 2-methyl-2-pentenylpotassium ^[18].
18. Schlosser, M.; Desponds, O.; Lehmann, R.; Moret, E.; Rauchschalbe, G.; *Tetrahedron* **1993**, *49*, 10175 - 10203.
19. Price, C.C.; Snyder, W.H.; *J. Am. Chem. Soc.* **1961**, *83*, 1773 - 1773.
20. Desponds, O.; Franzini, L.; Schlosser, M.; *Synthesis* **1997**, 150 - 152; Schlosser, M.; Porwisiak, J.; Mongin, F.; *Tetrahedron* **1998**, *54*, 895 - 900.
21. Davidson, M.; Parc, G.; Belguise, A.; Hellin, M.; Coussemant, F.; *Bull. Soc. Chim. Fr.* **1964**, 804 - 811.
22. Fischer, W.; Grob, C.A.; *Helv. Chim. Acta* **1978**, *61*, 2336 - 2350.
23. Manning, T.D.R.; Kropp, P.J.; *J. Am. Chem. Soc.* **1981**, *103*, 889 - 897.
24. Günther, H.; *NMR Spectroscopy : An Introduction*, Wiley, Chichester, **1980**, 61.