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STEREOSELECTIVE CONSTRUCTION OF QUATERNARY CARBON CENTERS. SYNTHESIS OF OPTICALLY ACTIVE γ,γ-DISUBSTITUTED γ-BUTYROLACTONES.

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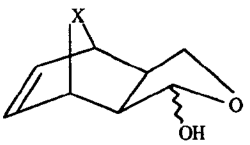
Abstract : *An unusually strong solvent effect has been observed on the diastereoselectivity of nucleophilic additions of bromoalkylmagnesium compounds to the lactols 2 and 3, allowing the formation of pure diastereoisomers of 1,4-diols. Homochiral γ,γ-disubstituted γ-butyrolactones could then be obtained after oxidation of these diols followed by a retro Diels-Alder reaction as illustrated by the synthesis of S-(+)-4,5-dimethyl-4-hexanolide.*

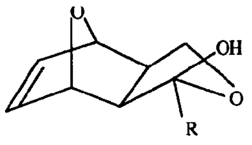
In the course of studies aimed at the development of stereoselective reactions induced by a thermolabile group, we have recently shown that the chelating ability of the oxygen bridge of the furan adduct **1a** had a great influence on the diastereoselectivity of its additions to various organometallic reagents [1]. A totally unexpected solvent effect had also been observed, leading to a reversal of selectivity when the addition of alkylmagnesium bromides to the lactol **1a** was carried out in diethyl ether instead of THF. Although the exact steric course of the reaction is not clear so far, we have been able to show that this effect is dependent on the nature of both the substrate and the reagent [2] since :

- A strong solvent effect is observed only when alkylmagnesium bromides are used, this effect being negligible with chloro or iodo Grignard reagents or other organometallics [3].
- The stereoselectivity of the addition of alkylmagnesium bromides to the lactol **1b**, where the oxygen bridge is replaced by a methylene group, is independent of the nature of the solvent, indicating that chelation is a factor of prime importance [4].

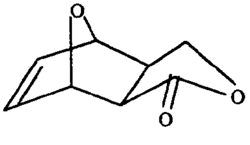
It seemed then interesting to check if such a solvent effect was restricted to the reactions of lactol **1a** or if it could be extended to the reactions of analogous substrates. In this communication we wish to report the asymmetric additions of organomagnesium reagents to the hemiketals **2** and **3** equivalents of γ-hydroxyketones, and the applications of these reactions to the synthesis of γ-lactones containing an asymmetric quaternary carbon center [5].



1a X=O **1b** X=CH_2



2 R=CH_3 **3** R=C_4H_9



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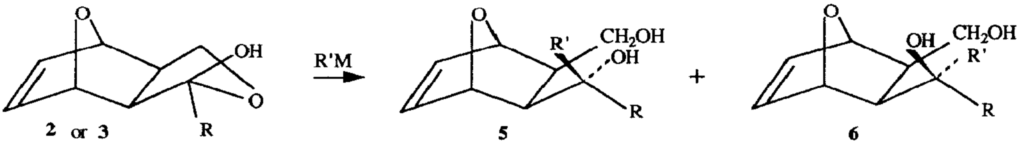
The hemiketals **2** and **3** were easily obtained by addition of methyl- or butyllithium to a THF solution of the corresponding lactone **4** [6]. As shown by ^{1}H NMR, only one diastereoisomer was formed, arising probably from the addition of the alkyllithium to the less hindered *re* face of the carbonyl group of the lactone. The additions of Grignard reagents to **2** and **3** were investigated in THF and diethyl ether and the ratio of resulting diastereoisomers (**5** : **6**) are summarized in Table 1. In all the cases (entries 1 to 10) the solvent was found to play an important role on the stereoselectivity of the addition of alkylmagnesium bromides to **2** and **3**. The solvent effect is even more pronounced here than the one already observed with lactol **1a** :

a) An inversion of selectivity, which was not observed with **1a** [7], appeared during the addition of alcynylmagnesium bromides to **2** (entries 7 and 8) ;

b) In several cases (entries 1,2,6,9,10) only one diastereoisomer was obtained so that a simple change of solvent allowed the synthesis of one or the other diastereoisomeric alcohols **5** or **6**. As far as we know, this is the most spectacular solvent effect ever observed for such additions of organomagnesium compounds to a carbonyl group.

Table 1. *Stereoselective additions of organometallics to lactols 2 and 3.*



Entry	Substrate	R'M a)	Solvent	Ratio **5** : **6** b)	Yield % c)
1	**2**	C_4H_9MgBr	THF	> 95 : 5	58
2	**2**	C_4H_9MgBr	Et_2O	< 2 : 98	59
3	**2**	C_2H_5MgBr	THF	90 : 10	75
4	**2**	C_2H_5MgBr	Et_2O	3 : 97	60
5	**2**	iPrMgBr	THF	no reaction	
6	**2**	iPrMgBr	Et_2O	< 5 : 95	52
7	**2**	$C_5H_{11}C{\equiv}C\text{-}MgBr$	THF	85 : 15	77
8	**2**	$C_5H_{11}C{\equiv}C\text{-}MgBr$	Et_2O	10 : 90	86
9	**3**	C_2H_5MgBr	THF	> 98 : 2	55
10	**3**	C_2H_5MgBr	Et_2O	< 2 : 98	72

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a) All the reactions have been performed at room temperature with an excess of Grignard reagent (4 to 8 equivalents). b) The ratios **5** : **6** have been determined on the ^{1}H NMR spectra at 250 MHz of the crude products by integration of the signals due to the bridgehead protons. The stereochemistry of the newly created quaternary carbon center has been determined later by examination of the ^{1}H NMR spectra of the lactones obtained by oxydation of **5** and **6**. c) Yields are given for pure compounds isolated by column chromatography on silicagel and have not been optimized.

This reaction has then been applied to the stereoselective obtention of γ-lactones containing a quaternary asymmetric carbon center. The diols **5** and **6** were oxidized with Jones reagent to afford with modest yields the lactones **7** and **8** (Table 2).

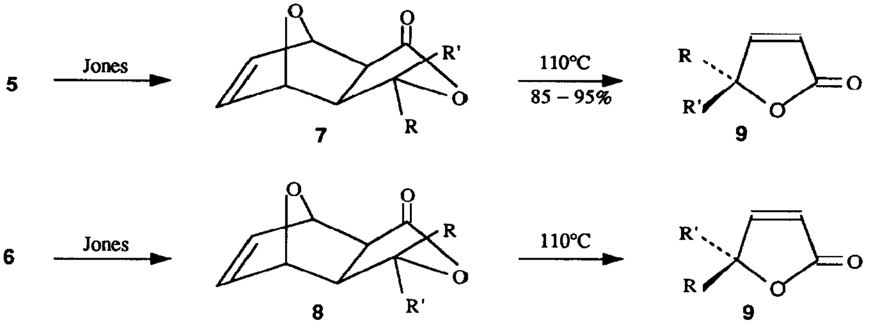
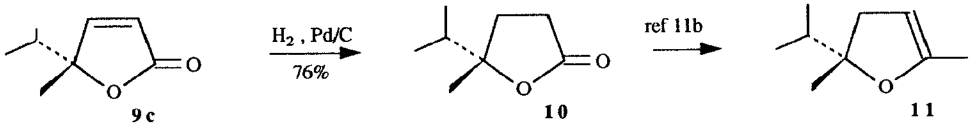


Table 2. *Obtention of γ,γ-disubstituted γ-lactones.*

Lactone	R	R'	Yield %	δCH_3 (ppm)
7a	CH_3	C_4H_9	56	1.40
7b	CH_3	C_2H_5	51	1.42
8a	CH_3	C_4H_9	56	1.49
8b	CH_3	C_2H_5	61	1.49
8c	CH_3	iPr	60	1.48
7d	C_4H_9	C_2H_5	63	
8d	C_4H_9	C_2H_5	53	

A first indication concerning the configuration of the quaternary carbon center of lactones **7a,b** and **8a-c** was given by the value of the chemical shifts of the methyl groups ($R = CH_3$) : as it was already found for monosubstituted analogous lactones [2], the signals due to these groups are more shielded (0.1 ppm) for the methyl in exo position. This stereochemistry has been confirmed for **7b** and **8b** by NOE experiments [8] and for homochiral **8c** by chemical transformations to a known lactone as shown below. The thermolysis of **7** and **8** in refluxing toluene gave rise with excellent yields to the γ,γ-disubstituted α,β-unsaturated lactones **9**.

Starting from the easily available optically active lactone **4** [9], homochiral disubstituted lactones could be obtained in a few steps as illustrated by the synthesis of S-(+)-4,5-dimethyl-4-hexanolide **10** a direct precursor of 2,3-dihydro-2-isopropyl-2,5-dimethylfuran **11**. This dihydrofuran, a sex specific compound for the beetle "Hylecoetus dermestoides" was isolated by Francke [10] and the two enantiomers have been synthetized [11]. As in racemic series, the addition of isopropylmagnesium bromide in ether to optically pure lactol **2** afforded the diol **6c**, $[\alpha]_D^{20} = -5$ ($CHCl_3$, $c = 1.7$) which was oxidized to the lactone **8c**, $[\alpha]_D^{20} = -106$ ($CHCl_3$, $c = 1.08$).



Thermolysis gave the butenolide **9c**, $[\alpha]_D^{20} = -44$ ($CHCl_3$, c = 0.83) which was hydrogenated to the S-(+)-4,5-dimethyl-4-hexanolide **10** [12] $[\alpha]_D^{20}$, = +10 ($CHCl_3$, c = 0.64) ; litt. [11b] $[\alpha]_D^{20} = -10.2$ ($CHCl_3$, c = 1.07) for the R-(-)enantiomer. The transformation **10** → **11** has already been described [11b].

Further applications of this efficient formation of asymmetric quaternary carbon centers are currently under investigation.

References and Notes

1) a) Bloch, R.; Gilbert, L. *Tetrahedron Lett.* **1987**, *28*, 423 ; b) Bloch, R.; Gilbert, L.; *J. Org. Chem.* **1987**, *52*, 4603.

2) Gilbert, L. Thesis, Orsay 1987.

3) After the completion of this work a similar solvent effect has been reported for the addition of organometallics to α-ketoamides : a) Kawanami, Y.; Fujita, I.; Ogawa, S.; Katsuki, T. *Chem. Lett.* **1989**, 2063 ; b) Kawanami, Y.; Katayama, K. *Chem. Lett.* **1990**, 1749. This solvent effect is also specific for alkylmagnesium bromides : Kawanami, Y. Personal communication.

4) Other factors such as the position of the Schlenk equilibrium and the degree of association of the Grignard reagent are also important factors for the steric course of such reactions : E.L. Eliel, "*Asymmetric Synthesis*" J.D. Morrison ed., Academic Press, Orlando, U.S.A. (1983) vol. 2, Chap. 5.

5) Asymmetric construction of quaternary carbon centers has been the subject of great interest during these last years. See Tomioka, K.; Cho, Y.S.; Sato, F.; Koga, K. *J. Org. Chem.* **1988**, *53*, 4094 and references there in.

6) The reaction was performed at -78°C with 1 equivalent of alkyllithium. In these conditions no trace of tertiary alcohols arising from the addition of two molecules of alkyllithium was observed. See Betancourt de Perez, R.M.; Fuentes, L.M.; Larson, G.L.; Barnes, C.L.; Heeg, M.J. *J. Org. Chem.* **1986**, *51*, 2039.

7) Bloch, R.; Gasparini, G. *J. Org. Chem.* **1989**, *54*, 3370.

8) The strong NOE observed for **7b** between the singlet methyl signal and the signal of the vicinal junction proton totally disappeared for **8b**.

9) Bloch, R.; Guibe-Jampel, E.; Girard, C. *Tetrahedron Lett.* **1985**, *26*, 4087.

10) Francke W.; Mackenroth, W.; Schröder, W. Levison, A.R. "Les colloques de l'I.N.R.A." **1982**, *7*, 85.

11) a) Redlich, H.; Xiang-Jun, J. Liebigs Ann. Chem. **1982**, 717 ; b) Mori, K.; Ebata, T.; Takechi, S. *Tetrahedron* **1984**, *40*, 1761.

12) An enantiomeric excess ee > 95% was assigned for **10** on the basis of ^1H NMR experiments in the presence of the chiral shift reagent $Eu(hfc)_3$.