

## Remote Asymmetric Induction. Stereo- and Enantioselective Synthesis of Symmetrical and Unsymmetrical 1,4-Diols.

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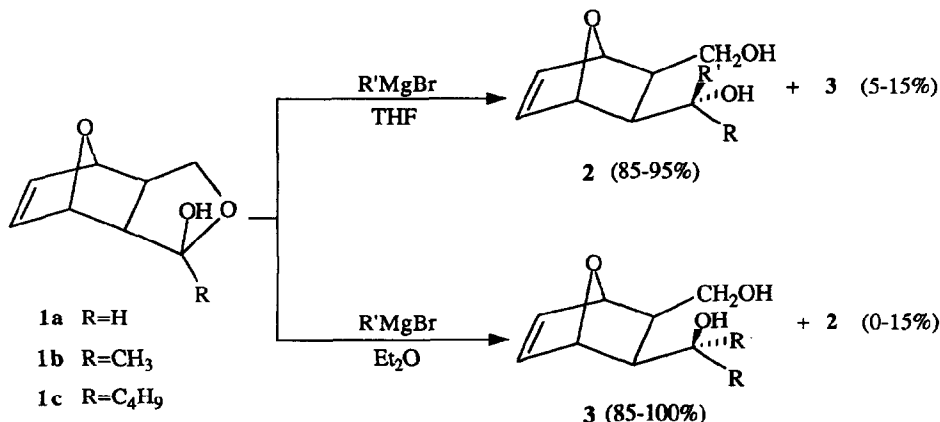
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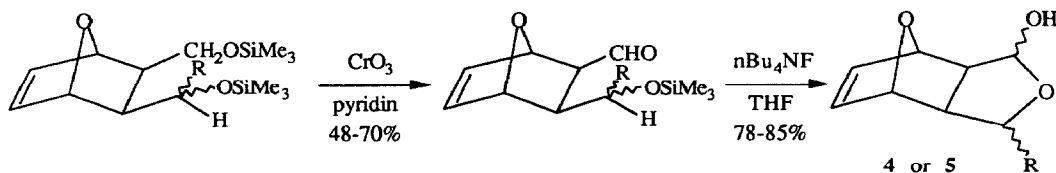
**Abstract :** Nucleophilic addition of Grignard reagents to the tricyclic lactols **4** or **5** provides with very high selectivity *syn* or *anti* 1,4-diols, so that, starting from the scalemic lactol **1a**, three of the four possible diastereoisomeric 1,4-diols **7** or **9** can be obtained. This new example of remote asymmetric induction is illustrated by the synthesis of optically pure (2*R*,5*R*)-2,5-hexanediol and (3*S*,6*R*)-4-decen-3,6-diol.

The control of the diastereoselectivity between remote carbon centers of acyclic molecules is still a challenging problem in practical organic synthesis. Actually, in contrast with the numerous works related to 1,2- or 1,3-stereocontrol <sup>1</sup>, the reports concerning selective 1,4-asymmetric induction are rare <sup>2</sup>. We report here a highly selective 1,4-relative asymmetric induction observed during the nucleophilic addition of Grignard reagents to the tricyclic lactols **4** or **5**, for which an intermediate rigid tridentate chelate is postulated. This process has been used for the synthesis of enantiomerically pure 1,4-diols which are very useful intermediates for the formation of 2,5-disubstituted pyrrolydines **3** or phospholanes **4**.

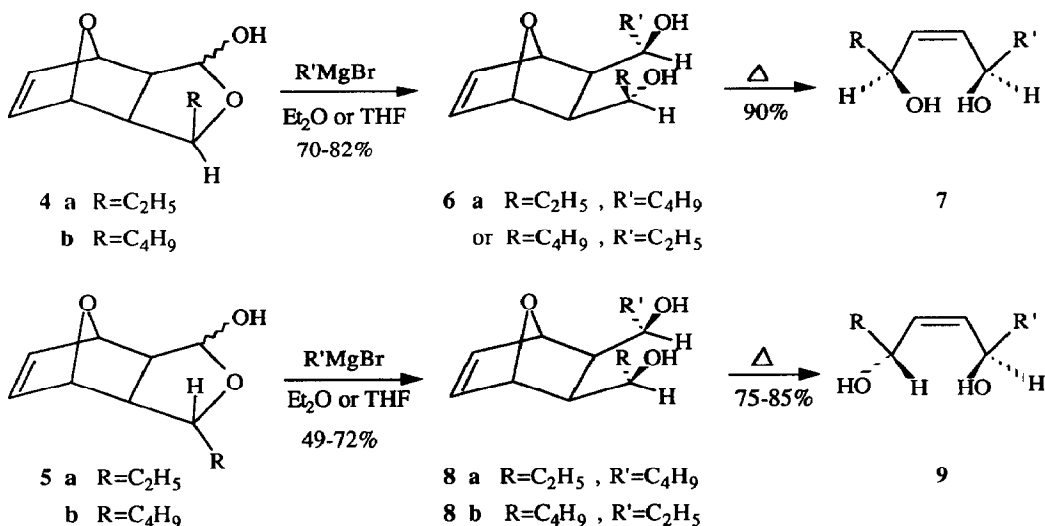
We have recently reported <sup>5</sup> that addition of alkylmagnesium bromides to the racemic lactols **1(a-c)** can be highly stereoselective and that a simple change of solvent from tetrahydrofuran to diethyl ether allowed the formation of one or the other diastereoisomeric diol **2** or **3**.



After protection of the two hydroxyl groups of **2a** or **3a** ( $R = H$ ) as trimethylsilyl ethers, the primary alcohol has been selectively oxidized with chromic anhydride in pyridine<sup>6</sup>. Deprotection of the secondary alcohol gives the substituted lactols **4** or **5**.

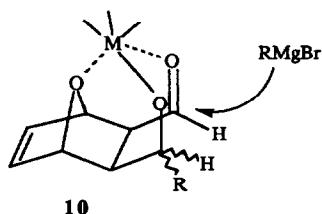


We have found that addition of alkylmagnesium bromides to the racemic lactols **4** or **5** gives in all cases only one diastereoisomer and that the configuration of the newly created asymmetric center is independent of the nature of the solvent and of the configuration of the first asymmetric carbinol carbon (scheme 1).



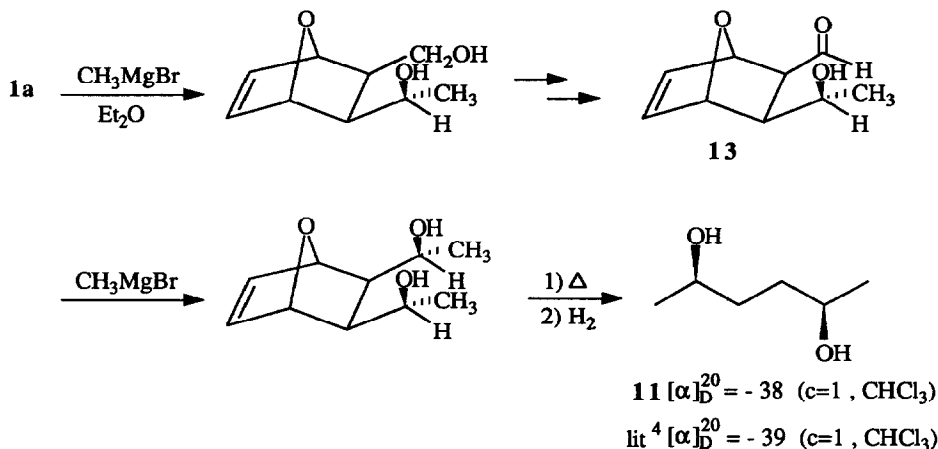
Scheme 1<sup>7</sup>

Addition of ethylmagnesium bromide to the lactol **4b** as well as addition of butylmagnesium bromide to **4a** lead to the same diastereoisomer **6a**. In contrast, addition of ethylmagnesium bromide to the lactol **5b** or addition of butylmagnesium bromide to **5a** affords two distinct diastereomers **8a** and **8b**. These results imply an attack of the Grignard reagents always on the same face of the carbonyl group, corresponding to the less hindered face of the tridentate chelate **10**.

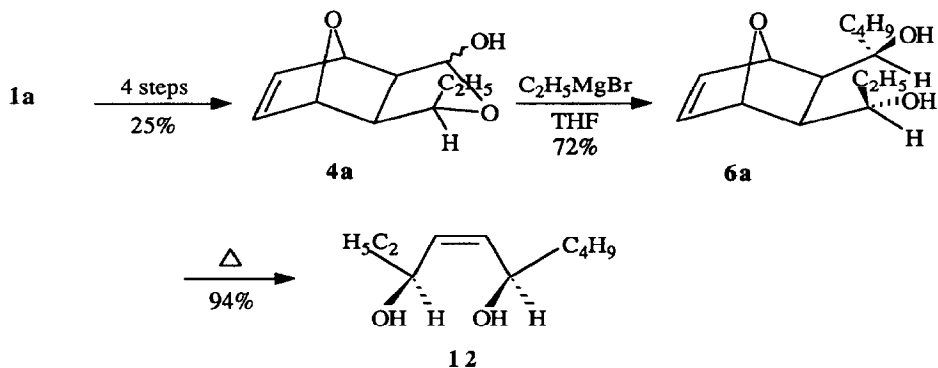


The presence of a free OH group is necessary since when the secondary alcohol is protected as a trimethylsilyl ether, the reaction is much less selective (ratios of stereoisomers from 1.5/1 to 3/1). Retro Diels-Alder reaction using flash thermolysis conditions (500°C, contact time < 1 s) provides from **6** or **8** one or the other diastereoisomeric unsaturated 1,4-diol **7** or **9**. Thus, starting from the enantiomerically pure lactol **1a**, easily available via an enzymatic pathway **8**, it could be possible to obtain three of the four possible diastereoisomers of unsaturated 1,4-diols (**7** or **9**) following the nature of the solvent (THF or Et<sub>2</sub>O) of the first Grignard reaction and the addition order of the two Grignard reagents. The versatility of this methodology has been illustrated by the synthesis of two optically pure 1,4-diols : (2*R*,5*R*)-2,5-hexane diol **11** and (3*S*,6*R*)-4-decen-3,6 diol **12**.

The obtention of the known diol **11** using this method is not very synthetically useful <sup>9</sup> but it is a good support to confirm the approach of the organomagnesium compound from the less hindered re face of the carbonyl group of the aldehyde **13**.



In contrast the syntheses of unsymmetrical 1,4-diols such as **12** or the corresponding saturated decanediol are very long processes and our method compares favourably with reported ones <sup>10</sup>. Thus, the lactol **4a**, obtained in four steps from the optically pure lactol **1a**, was treated with a solution of butylmagnesium bromide in tetrahydrofuran to provide the diol **6a** [ $\alpha$ ]<sub>b</sub><sup>20</sup> = +12, c = 1, CHCl<sub>3</sub>) as a unique diastereoisomer. Flash thermolysis at 500°C afforded with an excellent yield (3*S*,6*R*)-4-decen-3,6-diol **12**, [ $\alpha$ ]<sub>b</sub><sup>20</sup> = +14 (c = 0,8 ; CHCl<sub>3</sub>) :



The enantiomeric purity of 12 has been estimated higher than 95% by  $^1H$  NMR in the presence of a chiral shift reagent.

Applications of this methodology to the enantioselective synthesis of indolizidine alkaloids are currently underway in our laboratory.

#### References and Notes

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- 5) a) Bloch, R.; Gilbert, L. *Tetrahedron Lett.* 1987, 28, 423 ; b) Bloch, R.; Brillet, C. *Tetrahedron : Asymmetry* 1991, 2, 797.
- 6) Mahrwald, R.; Theil, F.; Schick, H.; Palme, M.J.; Nowack, H.; Weber, G.; Schwartz, S. *Synthesis* 1987, 1012.
- 7) All the products in this scheme are racemic but for clarity only one enantiomer is drawn.
- 8) Bloch, R.; Guibe-Jampel, E.; Girard, C. *Tetrahedron Lett.* 1985, 26, 4087.
- 9) As this work was in progress, a short but rather delicate synthesis of symmetrical 1,4-diols has been described : see reference 4.
- 10) For example, the synthesis of (5S,8S)-tridecane-5,8-diol has recently been made in 19 steps starting from D-mannitol : see reference 3b.