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WATER-PROMOTED CLAISEN SIGMATROPIC REARRANGEMENT USING GLYCO-ORGANIC SUBSTRATES. CHIRAL AUXILIARY- MEDIATED INDUCTION

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Abstract. The Claisen sigmatropic rearrangement with glyco-organic substrates is greatly accelerated in water. Moreover, the ability of glucose to function as a chiral auxiliary is illustrated in the preparation of *4-pentene-1,3-diol*, obtained for the first time in pure enantiomeric form.

The Claisen rearrangement of allylvinyl ethers provides an excellent route to γ, δ-unsaturated ketones or aldehydes and is a key step in the synthesis of some natural products.[1] It is therefore of great importance to lower the temperature of this thermal rearrangement. If we refer to our results on aldolisation[2] and the Diels-Alder reaction,[3, 4] the Claisen rearrangement, for which the $\Delta V^{\ddagger}$ is negative,[5] should be accelerated in water. Indeed, we have postulated that the reaction between two small hydrophobic molecules for which activation volume is negative must be accelerated in water, as it is under external pressure ; this effect, related to the well-known entropy-driven association of hydrophobic molecules in water (the hydrophobic effect), should tend to bring closer the two double bonds in the 1,5-dienyl system for the Claisen rearrangement. In fact, we cannot eliminate an effect of the high polarity of water on the possible dipolar transition state of the reaction.[6] In agreement with this hypothesis, recent studies on the non-enzymatic rearrangement of chorismate to prephenate revealed that the Claisen rearrangement of chorismate was 100 times faster in water than in methanol.[7] More recently, Grieco has described the accelerated influence of water as a solvent on the rate of the Claisen rearrangement.[8]

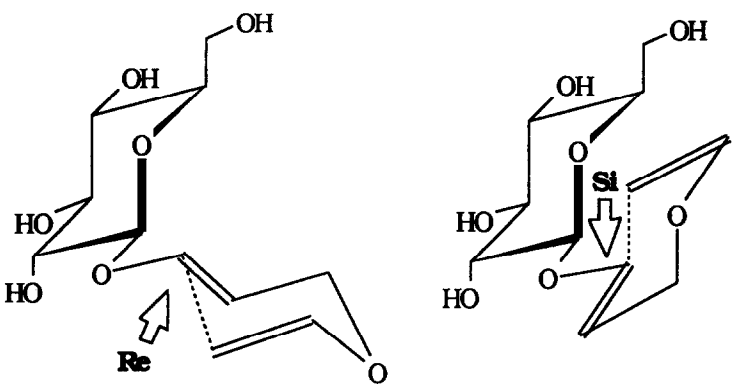
We report now[9] the preparation and the reactivity of the glyco-organic compound **4**, in which the glucose moiety, linked to an allylvinylether prone to rearrangement, induces both water solubility and chirality (scheme 2). Glucose functions as a chiral auxiliary, since it may be easily removed, after separation of the diastereomers formed, leaving a new enantiomerically-pure substance.

Sodium borohydride reduction of the easily available[3] aldehyde **1** gave the allylic alcohol **2** (90%), which was condensed with ethylvinylether in the presence of mercuric oxide[10] to afford **3** at room temperature (62%). After quantitative deacetylation

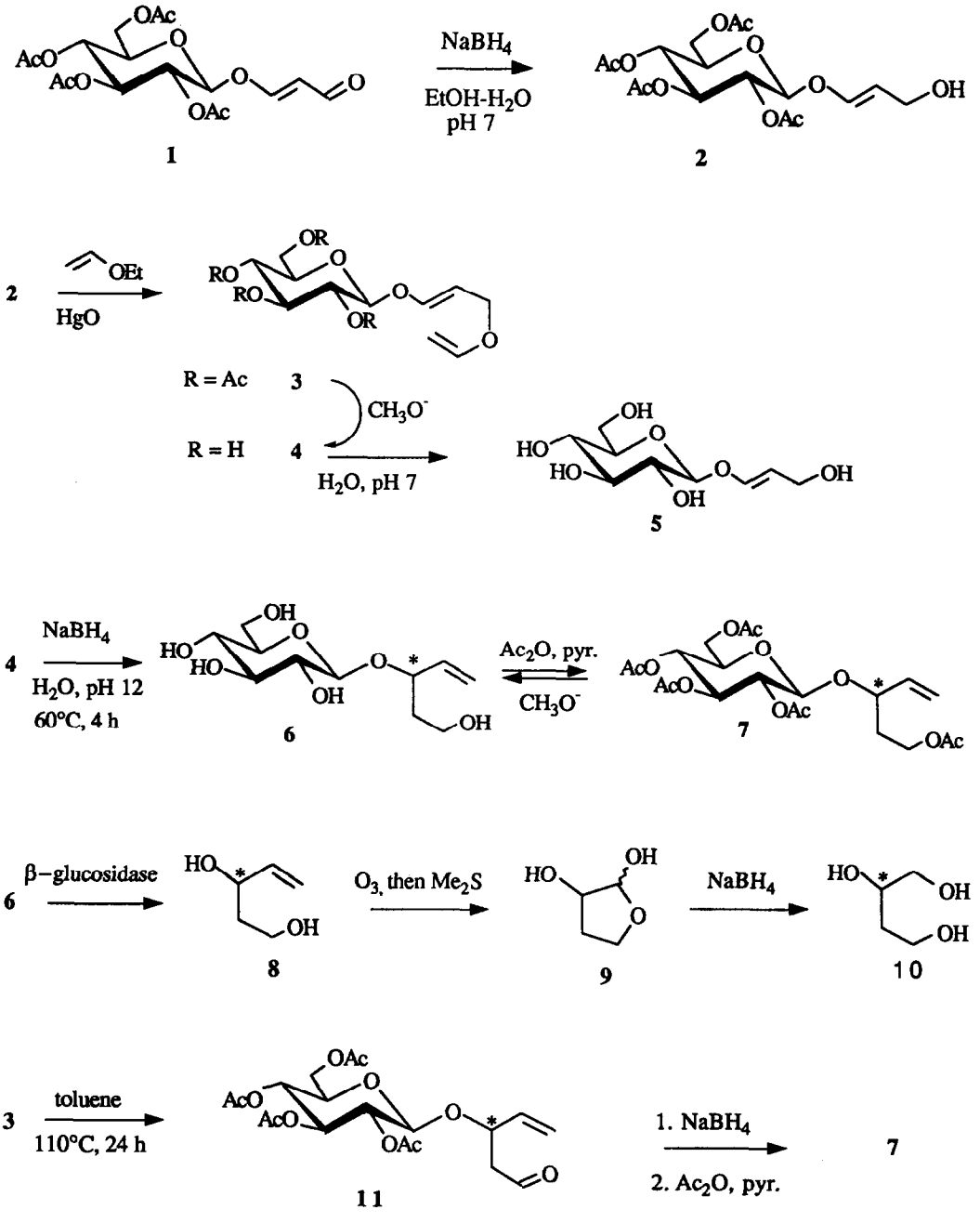
(CH_3ONa/CH_3OH) leading to the glyco-organic compound **4**, the Claisen rearrangement was conducted in water at pH 12 (NaOH) in the presence of $NaBH_4$ (2.5 eq.).[11] After stirring during 4 hours at 60°C, we obtained the alcohol **6** (80%) as a mixture of diastereomers (R/S = 60/40), which were acetylated (Ac_2O, pyridine) into the separable isomers **7**. Indeed, a fractional crystallization in diethylether gave pure (R)-**7**, which was deacetylated (CH_3ONa/CH_3OH) to afford pure (R)-**6**. The glyco-organic compound **6**, either as a mixture of (R) and (S) diastereomers arising directly from the Claisen rearrangement, or as the diastereomerically-pure (R) isomer, was hydrolysed overnight with a β-glucosidase (EC 3.2.1.21, 5.5 units/mg) to afford the diol **8** (90%). From the diastereomerically-pure (R)-**6** compound, we obtained enantiomerically-pure[12] (R) *4-pentene-1,3-diol* **8**. The absolute configuration of the newly created asymmetric carbon atom was determined after ozonolysis (O_3, then Me_2S) of **8**, which led to the *cis* and *trans* hemiacetals **9**, afterwards reduced ($NaBH_4$) into the triol **10**, the configuration of which was determined by polarometry.[14]

The Claisen rearrangement of **3** was performed in toluene and compared with the rearrangement of **4** in water: at the same temperature (80°C) and the same concentration (0.12 M), the rearrangement was achieved after 13 days in toluene, but only 1 hour in water. At 110°C, the Claisen rearrangement of **3** (24 hours, 92%) gave the ketone **11** as a mixture of diastereomers (R/S = 60/40). Reduction ($NaBH_4$), then acetylation (Ac_2O, pyridine) gave the same mixture of diastereomers **7** (R/S = 60/40) as in water.

The facial selectivity, both in toluene or in water, induced by the sugar moiety, was due to a preferred attack of the *re* face of the allylvinylether, avoiding the 1,3 *syn* diaxial interaction as depicted in scheme 1. It is interesting to note that the glucose moiety induced the same chirality as in the Diels-Alder reaction,[3] *i.e.* a preferred attack of the dienophile onto the *re* face of the dienyl ether of glucose.



Scheme 1: Facial selectivity in the Claisen rearrangement


OAc
AcO
AcO
O
OAc
O
1
NaBH4
EtOH-H2O
pH 7
OAc
AcO
AcO
O
OAc
O
OH
2
2
OEt
HgO
OR
RO
RO
O
OR
O
R = Ac
3
R = H
4
CH3O-
H2O, pH 7
OH
HO
HO
O
OH
O
OH
5
4
NaBH4
H2O, pH 12
60°C, 4 h
OH
HO
HO
O
OH
O
*
OH
6
Ac2O, pyr.
CH3O-
OAc
AcO
AcO
O
OAc
O
*
OAc
7
6
β−glucosidase
HO
*
OH
8
O3, then Me2S
HO
OH
O
9
NaBH4
HO
*
OH
OH
10
3
toluene
110°C, 24 h
OAc
AcO
AcO
O
OAc
O
*
O
11
1. NaBH4
2. Ac2O, pyr.
7

Scheme 2

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References and notes

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9. Preliminary results were presented during a meeting of the French Chemical Society in Palaiseau (Journées de Chimie Organique, Sept. 1989).
10. Vinylether exchange was generally performed in the presence of a Lewis acid, such as $Hg(OAc)_2$. Better results were obtained with mercuric oxide as the catalyst (0.2 equivalent of red HgO from Janssen Chemica).
11. At neutral or slightly basic pH and at 60 °C, **4** was cleaved into **5**; the addition of $NaBH_4$ allowed to reduce *in situ* the ketone arising from the Claisen rearrangement, and then to prevent its retroaldolisation to glucose.
12. For the preparation and use of racemic diol **8**, see ref. 13. The optically-pure diol **8** displays a specific rotation $[\alpha]_D$ = - 11° (*c* 1 in MeOH).
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14. The (R) configuration for triol **10** corresponds to a positive $[\alpha]_D$.[15]
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