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GLYCO-ORGANIC SUBSTRATES IN ORGANIC SYNTHESIS. PREPARATION OF A WATER SOLUBLE BUTADIENYL-ETHER AND ITS USE IN AQUEOUS CYCLOADDITION.

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Abstract : A chiral water-soluble butadienyl-ether containing free glucose as hydrophilic moiety was synthesized and used in aqueous cycloaddition reaction with methacrolein to afford through pure endo transition state, only two diastereoisomers from which the sugar could be removed by enzymatic hydrolysis.

Polar solvents has been known for a long time to increase stereospecificity in Diels-Alder reactions [1,2]. More recently, Breslow[3] and Grieco[4] reported aqueous cycloadditions with spectacular rate enhancements. The concentration of diene in water seemed to be crucial and the results depended on the reactants, indicating perhaps different origins of the effects of water in this type of cycloaddition. High concentrations could be achieved using carboxylate groups as the hydrophilic moiety, but this functionnality involves pH restrictions and is certainly not without effect on the energetic balance of the reaction. Moreover, this functionnal group suffers from the fact that it forms a permanent substituent in the products.

We propose as a general tool for organic syntheses in aqueous solution, a sugar-assisted solubilization of organic substrates in water. This concept, widely used in Nature, has allowed us also to take advantage of enzymatic catalysis in water, and affords new possibilities in organic synthesis in addition to the use of enzymes in organic solvents or biphasic systems when erratic results may obtain.

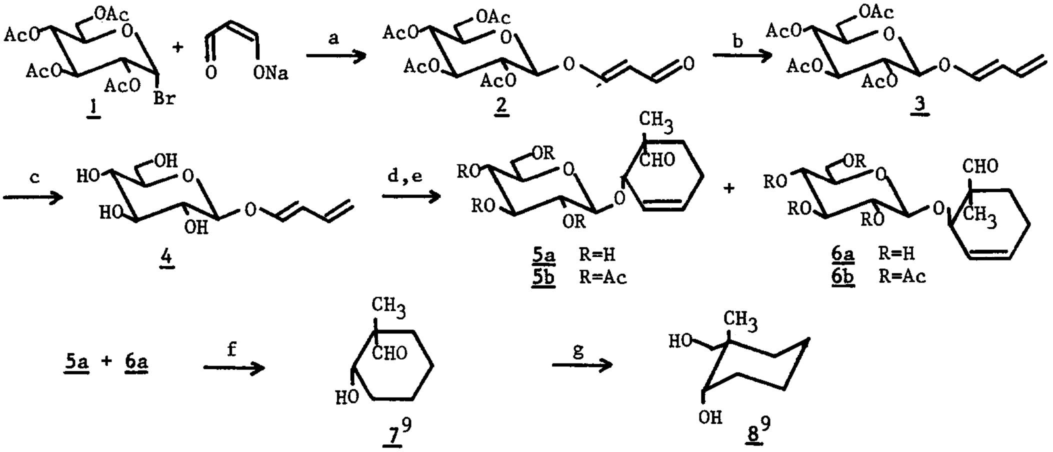
We describe here, as a model of glyco-organic substrate, the chiral water-soluble butadienyl ether <u>4</u> (scheme I). The formation of aldehyde <u>2</u> was stereoselective to give only the β-D-configuration[5], but the Wittig reaction could be conducted in two different ways. Starting from the β-anomer <u>2</u>, the reaction gave either the pure β-anomer <u>3</u> at -78°C or a mixture with the α-anomer predominant ($\alpha/\beta = 3$) at 25°C. The diene <u>4</u> obtained by deacetylation of compound <u>3</u> reacted with methacrolein[6] in water in 3.5h at 25°C whereas the acetylated derivative <u>3</u> required 15 days at 60°C in toluene. We chose methacrolein for the stereochemical stability of its adduct, to avoid further thermodynamical equilibration.

In fact, of the four possible adducts, a mixture of only two, was obtained in a 60/40 ratio (as determined by 400 MHz N.M.R.) from which the major diastereoisomer (m.p. 151°C, $(\alpha)_D^{20°}$ +77° (c 0.8, CH_2Cl_2)) was separated by cristallisation from ether after complete acetylation. The overall yield for the three steps starting from compound <u>3</u> to the mixture of the two acetylated adducts, <u>5b</u> and <u>6b</u>, was 90%. The stereochemical course of the reaction was established after hydrogenation on palladium on charcoal, acidic hydrolysis (H_2SO_4 1N 1h at 100°C) or enzymatic hydrolysis (β-glucosidase, 6h at 37°C in water) of the mixture 5a + 6a to afford a 60/40 enantiomeric mixture of compound 7 in which the hydroxyl and the carbonyl groups have been shown to have a cis relationship by N.M.R. examination after sodium borohydride reduction to the new cis-diol 8[7]. It must be emphasized that compound 7 and 8 could be obtained in a pure enantiomeric form starting either from 5a or 6a but their absolute configurations have not been established.

The above results may be ascribed to a pure endo transition-state with a 60/40 diastereofacial selectivity.

We expect that diene 4, besides its interest in synthesis, because of its high solubility in water, will be a very good model for the physico-chemical investigation of the considerable rate enhancement in this solvent.

SCHEME 1[8]



a. DMSO, 20°, 53%; b. $CH_2=PPh_3$, -78°, THF, 70%; c. NEt_3-MeOH-H_2O 8-1-1, 20°; d. $CH_2=C(CH_3)CHO$, H_2O; e. Ac_2O, pyridine; f. 1) H_2-Pd/C 2) H_2SO_4 1N 1h, 100° or β-glucosidase, H_2O, 37°; g. $NaBH_4$, EtOH-H_2O.

Acknowledgments.

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Notes and references.

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2. J.A. Berson, Z. Hamlet and W.A. Mueller, ibid.,1962, 84, 297.
3. D.C. Rideout and R. Breslow, ibid., 1980, 102, 7816.
4. P.A. Grieco, P. Garner and Zhen-min He, Tetrahedron Lett., 1983, 24(18), 1897.
5. For a similar reaction see R.C. Gupta, P.A. Harland and R.J. Stoodley, J. Chem. Soc. Chem. Comm., 1983,754.
6. The cycloaddition was conducted using 0.5M solutions of diene and three equivalents of methacrolein.
7. The new cis-diol 8 was shown by N.M.R. measurements to be an enantiomeric mixture using the chiral shift reagent Eu(hfc)$_3$. The cis configuration was ascertained by the presence of an axial hydroxyl group. The known trans isomer has been shown[10] to have both the hydroxyl and hydroxymethyl groups in equatorial positions.
8. Compounds 2, 3, 5b, 6b and 8 have been fully characterized by spectral means and satisfactory elemental composition. 2 : m.p. 135°C, $(\alpha)_D^{20°}$ -22° (c 1, CH_2Cl_2); 3 : m.p. 153°, $(\alpha)_D^{20°}$ -13° (c 1, CH_2Cl_2)
9. 60/40 enantiomeric mixture.
10. W.B. Smith, J. Org. Chem., 1979, 44(10), 1631.

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