discussion. H.C. and J.C. thank the New York State Sea Grant, NSF INT14133, and NIH CA24487 for financial support.

Registry No. **1a**, 97068-30-9; **1b**, 97068-31-0; **2**, 6377-18-0; **3**, 34170-23-5; **4**, 106544-47-2; **5**, 106544-48-3; **6a**, 106544-49-4; **6b**, 106544-50-7; **7b**, 106544-51-8; **8a**, 106544-53-0; **8b**, 106544-54-1; **9a**, 106622-98-4; **9b**, 106622-99-5; **10a**, 106544-55-2; **11a**, 53958-79-5; **13a**, 106544-52-9; **14**, 106544-56-3.

Supplementary Material Available: Tables of fractional coordinates and thermal parametes, bond distances, bond angles, and torsion angles for **1a** (16 pages). Ordering information is given on any current masthead page.

Aqueous Cycloadditions Using Glyco-Organic Substrates. 1. Stereochemical Course of the Reaction[1]

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Received July 31, 1986

New water-soluble *trans*-butadienyl ethers were synthesized by using free glucose as the hydrophilic part. Aqueous cycloaddition with a variety of dienophiles showed rate and stereoselectivity enhancement in comparison with similar peracetylated dienes in organic solvents. After cycloaddition and eventually functional group manipulations, the sugar moiety was smoothly removed by enzymatic hydrolysis to give highly functionalized chiral cyclohexane derivatives. In this way, as a model, the new (1*S*,2*S*)-2-(hydroxymethyl)-2-methylcyclohexanol was prepared.

Introduction

In view of the widespread occurrence in nature of highly functionalized six-atom rings, (4 + 2) cycloaddition reactions continue to provide inventive strategies for natural product elaboration. Their successes are due to the perfect cis stereospecificity, the good regioselectivity, and the fairly good yields which are usually obtained. However, for preparative purposes, the normal reaction requires activated dienes (with electron-donating substituents) and activated dienophiles (with electron-withdrawing substituents) to proceed at temperatures compatible with the thermal stability of more and more complex targets. Therefore, intensive efforts have been made concerning new modes of activations of both partners,[2] new catalysts,[3] as well as theoretical studies to elucidate mechanistic aspects. In this connection, there are extensive studies of the influence of solvents on the kinetic and stereochemical outcome of cycloaddition. Several correlations of rate and/or endoselectivity with solvent parameters[4-6] have been published, but none included water, so that the prevailing opinion seems to be, more or less, that the influence of the solvent—independent of the system investigated—was relatively small.[4,7] In contrast, in 1980, Breslow's group[8] reported in a pioneering paper remarkable rate and stereoselectivity enhancements when the cycloadditions were conducted in water in comparison with organic solvents. It was also pointed out that such reactions could be achieved on a preparative scale without loss of stereoselectivity, even if one of the reactants was only sparingly soluble in water. Subsequently, Grieco et al.[9] reported utilization of dienes attached to a carboxylate group in preparative aqueous cycloaddition.

Although water has been considered as a possible solvent in Diels–Alder reactions ever since their discovery,[10] its poor solvent properties for dienes made it look unpromising. Consequently, in numerous papers on the subject water is absent from the list of solvents under investigation, undoubtedly a fact which discouraged its utilization. Since Breslow's paper, the effects of water have been much debated.[11] Undoubtedly, they cannot be explained only by the polarity of water, as the reaction of cyclopentadiene with methyl acrylate gave less endo adduct in formamide (ϵ 109) and *N*-methylacetamide (ϵ 133) than in water[12] (ϵ 80). Moreover, the lack of endo selectivity in water in the case of the polar dienophile PhSOCH=CHCO$_2$H[13] suggested a relation to the hydrophobic effect. This has been confirmed and clearly demonstrated using solutions of "structure-breaking" or "structure-making" salts in the case of the reaction of cyclopentadiene with methyl vinyl ketone.[8] When two nonpolar molecules are dissolved in water, they tend to aggregate. This entropy-driven association is well-known and is of importance in biological chemistry.[14] So, the rate enhancement could be the result of an entropy-favorable process. The question now arises whether the stereoselectivity could have the same origin. In 1974, Dack[15] stressed the importance of considering the activation volume $\Delta V^{\ddagger}$, in relation with the solubility parameter δ of the solvent for chemical reactivity. Water, with the highest known solubility parameter (δ 23 cal$^{1/2}$ mL$^{-3/2}$), then appeared as a solvent of choice for a reaction with negative activation volume between two nonpolar

(1) For a preliminary report, see: Lubineau, A.; Queneau, Y. *Tetrahedron Lett.* **1985**, *26*(22), 2653.
(2) For a review on activation of 1,3-diene and use in Diels–Alder reactions, see: Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 853.
(3) Lazlo, P.; Lucchetti, J. *Tetrahedron Lett.* **1984**, *25*, 2147 and references therein.
(4) Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779.
(5) Berson, J. A.; Hawlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297. Stefain, A. P.; Wong, K. F.; Eckert, C. A. *J. Am. Chem. Soc.* **1968**, *90*, 1694.
(6) Firestone, R. A.; Saffar, S. G. *J. Org. Chem.* **1983**, *48*, 4784.
(7) Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1984**, *49*, 3001.
(8) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.
(9) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, *48*, 3139. Grieco, P. A.; Yoshida, K.; He, Z.-m. *Tetrahedron Lett.* **1984**, *25*, 5715.
(10) Diels; Alder *Justus Liebigs Ann. Chem.* **1931**, *490*, 243. Woodward, R. B.; Baer, H. *J. Am. Chem. Soc.* **1948**, *70*, 1161.
(11) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239.
(12) Samii, A. A.; Savignac, A.; Rico, I.; Lattes, A. *Tetrahedron* **1985**, 3683.
(13) Proust, S. M.; Ridley, D. D. *Aust. J. Chem.* **1984**, *37*, 1677.
(14) Eagland, D. In *Water, A Comprehensive Treatise*; Franko, F., Ed.; Plenum: New York, 1975. Tanford, C. *Hydrophobic Effect*; Wiley: New York, 1980.
(15) Dack, M. R. J. *J. Chem. Ed.* **1974**, *51*(4), 233.

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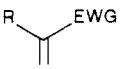
Table I. Cycloadditions Using Dienophiles under Varying Conditions



diene	R	EWG	temp, °C	time, h	solvent	yield, %	*endo-re*, %	*endo-si*, %	*exo-re*, %	*exo-si*, %	*re:si*	endo:exo
4	CH_3	CHO	20	3.5	water	90	60	40			60:40	100:0
4	H	CHO	20	3	water	92	58	42			58:42	100:0
4	H	CO_2Me	60	18	water	66	73	27			73:27	100:0
6	CH_3	CHO	20	6	water	78	34	59	2	5	36:64	93:7
3	CH_3	CHO	80	168	toluene	80	54	33	8	5	62:38	87:13
5	CH_3	CHO	80	168	toluene	94	30	54	5	11	35:65	84:16

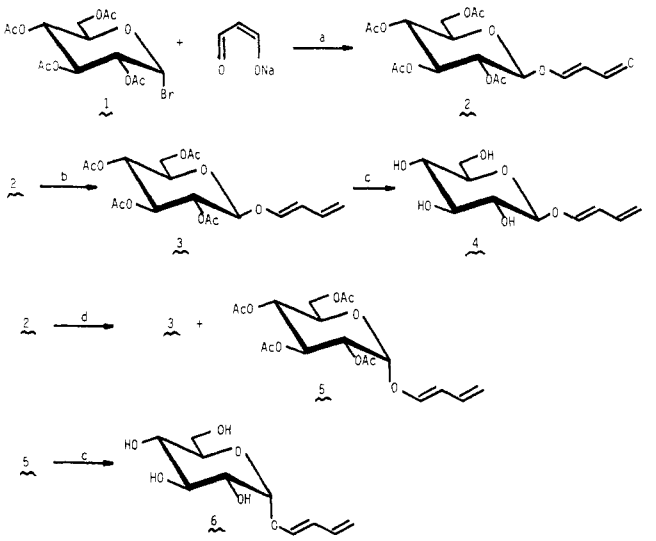
substrates. The prediction was made that "solvent internal pressure acts on the rate of nonpolar reactions in the same direction as external pressure". This strongly suggests that endo selectivity in aqueous cycloadditions could have the same origin as the rate enhancement, as the more compact endo transition states are favored by external pressure. Moreover, one of us has recently shown[16] that this prediction was also true for another reaction, the aldol condensation of the silyl enol ether of cyclohexanone with benzaldehyde, which, compared with cycloaddition, has nothing in common but the hydrophobic character of the reactants and a negative activation volume. This reaction was shown to proceed in a water solution, without catalyst, with the same stereoselectivity and comparable speed as under 12 kbar pressure. It is remarkable that this stereoselectivity is the reverse of that observed under conditions of acidic catalysis.

Quite obviously, to confirm these hypotheses on the role of water, we need to know the thermodynamics of aqueous cycloaddition. These will be the subject of a forthcoming paper. While the poorly soluble cyclopentadiene (10 mM in water) is quite reactive, totally insoluble dienes, such as, for instance the peracetylated derivative **3** gave no reaction in water even with a completely water-miscible dienophile like methacrolein. We conclude that both reactants should be fairly soluble for preparative work. In this opening survey study, we want to report here on the advantages of glyco–organic substrates, i.e., fairly soluble (0.5 M) compounds, built from hydrophobic organic moiety attached to hydrophilic free sugars. As shown by preliminary experiments, such dienes show great rate enhancement in water compared with methanol, due to an increase in both the second-order rate constant and concentration term in the rate law.[17]

The main requirements of this scheme are (1) the possibility of preparing on a large scale, a versatile water-soluble diene and/or dienophile and (2) the possibility of removing as smoothly as possible the hydrophilic part after the reaction and eventually after functional group manipulations on the adducts.

We have designed a new alkoxy diene, the group alkoxy being a glucose unit, bearing four hydroxyl groups. The butadienyl part is linked in anomeric position to facilitate the removal of the sugar moiety either by acidic hydrolysis or better, with a glucosidase in neutral conditions. These glyco–organic substrates allow functional group manipulations on the lypophilic part while the sugar gave water solubility and eventually asymmetric induction.[18] Moreover, at one stage of the synthesis, when the product is still water-soluble, one may envisage to intercalate an enzyme-mediated reaction. This gives new possibilities to use enzymes in organic synthesis in addition to the use of enzymes in organic solvents or biphasic medium where erratic results may be observed.

Scheme I[a]



[a] (a) Me_2SO, 20 °C, 4 h; (b) $Ph_3P{=}CH_2$, THF, −78 °C, 0.5 h; (c) MeOH–NEt_3–H_2O, 8:1:1, 20 °C, 16 h; (d) $Ph_3P{=}CH_2$, THF, 20 °C, 0.5 h.

Results

(A) Synthesis of Water-Soluble Dienes (Scheme I). Treatment of the readily available acetobromoglucose **1** in Me_2SO solution with the sodium salt of malonaldehyde[19] gave the β-glucoside **2**, isolated in 56% yield by direct crystallization. Some years ago, we had shown[20] that Wittig reaction on β-alkoxy α,β-unsaturated aldehydes gave *trans*-butadienyl ethers. In the same way, addition of "salt-free" methylenetriphenylphosphorane to aldehyde **2** at −78 °C in an oxolane–toluene mixture gave the diene **3** with the expected β-configuration (only traces of the α-isomer **5** were detected) in 83% yield. Reaction at room temperature gave in 72% total yield, a 3:1 mixture of glucosides with predominance of the α-anomer **5**. This isomerization to the more stable α-anomer at room temperature suggests the operation of an equilibrium at some step of the reaction. As the final β-dienyl ether is stable under Wittig conditions, the anomerization must occur at the level of the unsaturated aldehyde. Final deacetylation in a (8:1:1) NEt_3–MeOH–H_2O mixture gave dienes **4** or **6** in essentially quantitative yields.

(B) Stereochemical Course of the Cycloadditions. The results are summarized in Table I. The cycloaddition

(16) Lubineau, A. *J. Org. Chem.* **1986**, *51*, 2142.

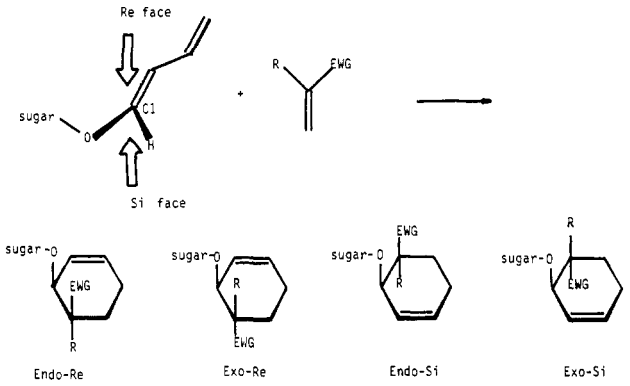
(17) The actual second-order rate constant for the cycloaddition of diene **3** with methyl vinyl ketone was measured at 20 °C in methanol (1×10^{-5} M^{-1} s^{-1}) and in water (20×10^{-5} M^{-1} s^{-1}).

(18) For an excellent review on asymmetric cycloadditions reactions, see: Paquette, S. L. *Asymmetric Synthesis*; Academic: New York, **1984**, Vol. 3.

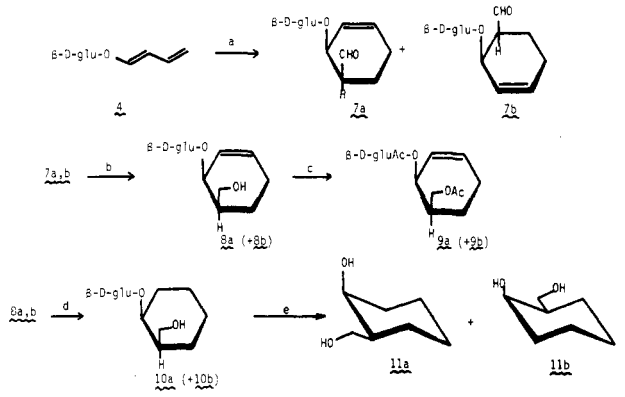
(19) Hüttel, R. *Ber.* **1941**, *12*, 1827. George, W. O.; Mansell, V. G. *J. Chem. Soc. B* **1968**, 132.

(20) David, S.; Lubineau, A.; Vatèle, J.-M. *Nouv. J. Chim.* **1980**, *4*, 547.

Scheme II



Scheme III[a]

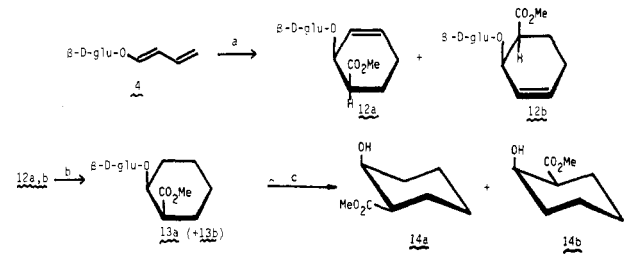


[a] (a) CH_2=$CHCHO$, H_2O, 20 °C, 3.5 h; (b) $NaBH_4$, phosphate buffer pH 7, 0 °C, 0.5 h; (c) Ac_2O, pyridine, 20 °C, 24 h; (d) H_2, Pd/C, MeOH–AcOEt, 65:35, 20 °C, 5 h; (e) H_2SO_4, 1 N, 100 °C, 17 h or β-glucosidase, H_2O, 37 °C, 3.5 days.

creates two new chiral centers and thus leads to four diastereoisomers, which can be named from mechanistic considerations about the transition states. Firstly, endo or exo transition states, respectively, lead to a cis or trans disposition of substituents in the newly formed ring. Secondly, the diene is prochiral, with two faces, *re* or *si*, as defined with reference to the prochiral carbon atom C-1 (linked to the oxygen atom) of the dienyl moiety. Endo or exo addition, either on the *re* or *si* faces leads to four diastereoisomers, accordingly labeled *endo-re*, *exo-re*, *endo-si*, and *exo-si* (Scheme II).

B.1. Aqueous Diels–Alder Reactions of Diene 4. First we examined the cycloaddition of diene **4** with acrolein (Scheme III). Diene **4** (0.5 M) reacted with 4 equiv of acrolein within 3 h at room temperature in water to give a mixture of only two products **7a,b**. The aldehyde function was then reduced by sodium borohydride in buffer solution to avoid epimerization, and the resultant polyols **8a,b** were acetylated (pyridine–Ac_2O) to give **9a,b**. At this stage, ^1H NMR ($CDCl_3$, 250 MHz) examination showed unambiguously a mixture of only two products in a 60:40 ratio, from which the major stereoisomer **9a** could be obtained in a pure state by fractional crystallization. To determine the stereochemical course of the reaction, the mixture of olefinic polyols **8a,b** was reduced (H_2/Pd) and the glucose moiety was removed, either by acidic hydrolysis (H_2SO_4, 0.5 M, 1 h at 100 °C) or, better, by treatment with β-glucosidase in water. Only the known[21] *cis*-2-(hydroxymethyl)cyclohexanol (**11a,b**) was obtained, which confirmed the pure endo transition state for aqueous

Scheme IV[a]



[a] (a) CH_2=$CHCO_2Me$, H_2O, 60 °C, 18.5 h; (b) H_2, Pd/C, EtOH/AcOEt, 2:1, 20 °C, 6.5 h; (c) β-glucosidase, H_2O, 37 °C, 7 days.

cycloaddition of diene **4** with acrolein. The structure of **11a,b** was secured by comparison with an authentic sample of *cis*-2-(hydroxymethyl)cyclohexanol[22] prepared by catalytic hydrogenation (H_2, PtO_2) of 2-(methoxycarbonyl)-cyclohexanone followed by lithium aluminium hydride reduction after separation of the two diastereoisomeric cyclohexanol by silica gel chromatography (ether–hexane, 1:3). **11a,b** was shown to be identical with the cis stereoisomer as shown by the superimposable NMR spectra (D_2O, 250 MHz). Coupling constants and chemical shifts are identical with those published in ref 21 for both cis and trans stereoisomers. As both cis enantiomers **11a** and **11b** are known[21] in the pure state, the measurement of the optical rotation of our mixture indicated that we had in hand a 58:42 mixture of **11a**:**11b**, and thus the major isomer **9a** was an *endo-re* adduct.

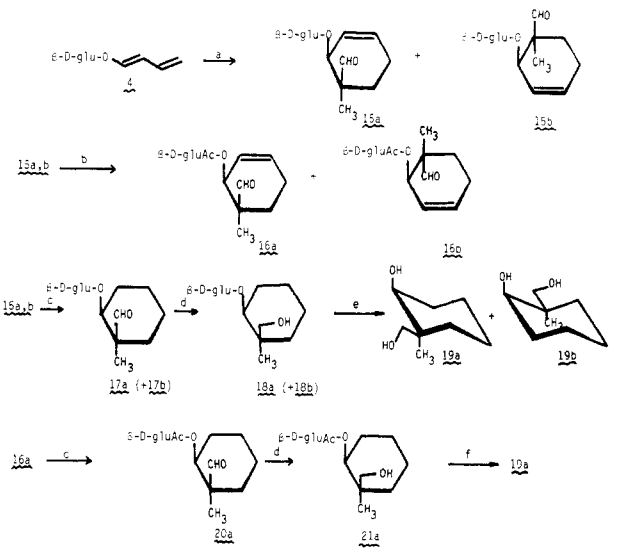
Then we turned to methyl acrylate reportedly a relatively poor dienophile (Scheme IV). Diene **4** required 18.5 h at 60 °C in water for completion of the reaction. At this stage, two products **12a,b** could be detected by ^1H NMR (CD_3OD, 250 MHz) examination in a 70:30 ratio and the major diastereoisomer **12a** could be obtained in a pure state by fractional crystallization (acetone). Combustion analysis gave not satisfactory results as it may happen for free sugars, but ^1H NMR confirmed the structure. After catalytic hydrogenation, enzymatic hydrolysis gave the known[22] *cis*-2-(methoxycarbonyl)cyclohexanol (**14a,b**). The structure of **14a,b** was secured by comparison of the diol obtained after lithium aluminium hydride reduction with an authentic sample of *cis*-2-(hydroxymethyl)cyclohexanol as above. No signal corresponding to the trans isomer could be detected in the NMR spectrum (D_2O, 250 MHz). Optical rotation measurement indicated a 73:27 ratio with the *endo-re* as the major adduct.

Finally, methacrolein was used as dienophile (Scheme V). In this case, functional group manipulations—acetylation and reduction—are without incidence on the stereochemistry of the adducts as no epimerizable carbon atom is involved. The reaction of diene **4** with 4 equiv of methacrolein occurred within 3.5 h in water at room temperature. After peracetylation, ^1H NMR ($CDCl_3$, 400 MHz) examination still showed the presence of only two products **16a,b** in a 60:40 ratio, and once more, the major stereoisomer **16a** could be obtained in a pure state by fractional crystallization (ether). Catalytic hydrogenation of **15a,b** followed by sodium borohydride reduction and cleavage of the sugar moiety by acidic or enzymatic hydrolysis gave a mixture of the new *rel*-(1*S*,2*S*)-2-(hydroxymethyl)-2-methylcyclohexanol (**19a,b**). The pure enantiomer (1*S*,2*S*)-**19a** was prepared in the same way from **16a**. Assignment of absolute stereochemistry was made using spectral and optical data. Comparison of the ^1H

(21) Lemieux, R. U.; Brewer, J. T. *Carbohydrates in Solutions*, Advances in Chemistry 117; American Chemical Society; Washington, DC, 1973.

(22) Torne, P. G. *Rev. R. Acad. Cienc. Exactas Fis. Nat. Madrid* **1966**, *60*, 419; *Chem. Abstr.* **1967**, *66*, 55082w.

Scheme V[a]



[a] (a) CH_2=$CH(CH_3)CHO$, H_2O, 20 °C, 3.5 h; (b) Ac_2O, pyridine, 20 °C, 24 h; (c) H_2, Pd/C, EtOH–AcOEt, 2:1, 20 °C, 24 h; (d) $NaBH_4$, H_2O, 5 °C, 2 h; (e) H_2SO_4, 1 N, 100 °C, 18.5 h or β-glucosidase, H_2O, 37 °C, 24 h; (f) H_2SO_4, 1 N, 100 °sC, 4 h.

NMR spectra of the major **16a** and the minor **16b** diastereoisomers showed as with acrolein and methyl acrylate a slightly greater deshielding of the anomeric proton of glucose unit and a smaller separation of olefinic protons for each major isomer. On the basis of a same modification of conformation in the three cases, the *endo-re* configuration could be assigned to **16a**. Moreover, the optical rotations for the three cyclohexane derivatives **11a**, **14a**, and **19a** are consistant with the Brewster procedure[23] for determining molecular rotation in cyclic compounds. According to this method, if the conformation of the cyclohexane ring is not changed, introduction of an axial methyl group in **19a**, compared to **11a**, should not change significantly the molecular rotation. In fact, in the three cases, we observed the same conformation with an axial hydroxyl group (as shown by ^1H NMR) and comparable figures for the all positive molecular rotation for the three substituted cyclohexanols: **11a**, $[MR]^{20}_D$ +46° (water); **14a**, $[MR]^{20}_D$ +50° (Et_2O); **19a**, $[MR]^{20}_D$ +31° (water).

B.2. Aqueous Diels–Alder Reactions of Diene 6 with Methacrolein (Scheme VI). The reaction of diene **6** with methacrolein required 6 h at room temperature for completion. In this case, endo selectivity is eroded, and the facial selectivity is reversed in comparison with the β-anomer **4**. After peracetylation, the mixture was directly examined by ^1H NMR ($CDCl_3$, 250 MHz). This indicated the presence of four adducts *endo*-**24a,b** and *exo*-**25a,b** in a 15.8:27:1:2.2 ratio as judged by integration of aldehyde and methyl signals. The ratio endo/exo was confirmed after catalytic hydrogenation of the mixture **22a,b** + **23a,b**, followed by sodium borohydride reduction and acidic or enzymatic cleavage of the sugar moiety to yield a mixture of the new diols **19a,b** as above along with the known[24] **30a,b** in a 13.2:1 ratio of **19a,b**/**30a,b**. The assignment of the facial selectivity in the endo transition state (27:15.8) in favor of **24b**, results from a negative optical rotation of the mixture **19a,b** (vide supra), whereas in the case of the minor exo transition state, the 2.2:1 ratio in favor of **25b** rests on the assumption that there is no reversal of the facial selectivity for endo and exo transition states as it was shown previously for numerous asymmetric cycloadditions onto dienyl ethers link to a sugar.[25] The reversal of the facial stereoselectivity in the α-series in comparison with the β-series could be rationalized by invoking similar extended conformations **4A** and **6A** which are preferred to the staggered conformations **4B** and **6B** (Scheme VII). In each case, the dienophile adds to the π-face of the dienyl ether from the same side with reference to the glucose unit, that is from the side of the hydroxyl group in the two position, the *re* face in the β-anomer and the *si* face in the α-anomer.

B.3. Reaction of the Peracetylated Diene 3 with Methacrolein in Toluene (Scheme VIII). The reaction of diene **3** with methacrolein in toluene required 1 week at 80 °C for completion. Direct examination of the mixture by ^1H NMR ($CDCl_3$, 250 MHz) indicated a mixture of *endo*-**16a,b** and *exo*-**31a,b** stereoisomers in a 6.6:1 ratio of endo/exo, and a facial diastereoselectivity of 1.63:1 for **16a**/**16b** and 1.5:1 for **31a**/**31b**. These assignments were made using H-1 of glucose, methyl, and aldehyde signals by comparison with the products of aqueous cycloaddition and consecutive peracetylation.

Here again, the facial selectivity in the minor exo transition state was not rigorously demonstrated but was based on previous experiments.[25]

B.4. Reaction of the Peracetylated Diene 5 with Methacrolein in Toluene. The reaction of diene **5** with methacrolein required, as for the diene **3**, 1 week at 80 °C for completion. ^1H NMR analysis indicated a mixture of *endo*-**24a,b** and *exo*-**25a,b** (identical with those obtained in aqueous cycloaddition and consecutive peracetylation) in a 5.7:1 ratio of endo/exo with a facial diastereoselectivity of 1:1.7 for **24a**/**24b** and 1:2.6 for **25a**/**25b**.

Conclusion

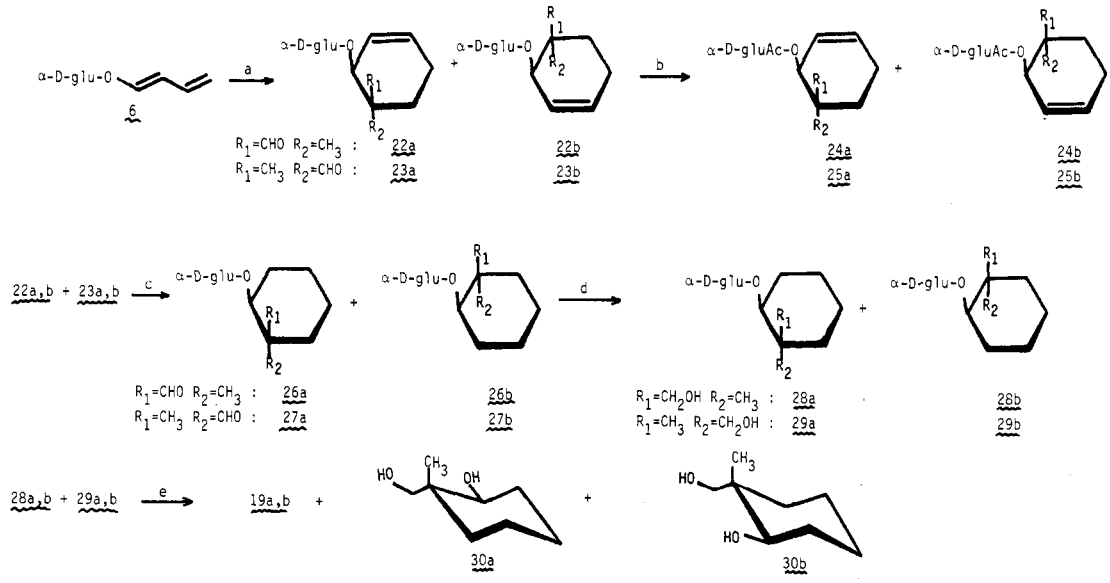
We have shown that glyco–organic substrates built from a lipophilic diene link in an anomeric position to a free sugar react in aqueous cycloaddition to give good yields of adducts through pure endo transition states more rapidly and at a much lower temperature than the corresponding peracetylated lipophilic diene in organic solvent. The easy removal of the sugar part by enzymatic hydrolysis yielded highly functionalized chiral cyclohexane derivatives which can be eventually further elaborated. Beyond the preparative aspect of such glyco–organic substrates, we think that such compounds, because of their high water solubility, can serve as chemical probes to study the water structure and gain some insight into the hydrophobic effect. We are currently working in this area by studying the thermodynamics of such reactions in water and in mixed solvents by varying the structure of the sugar.

Experimental Section

General Considerations. When the temperature of a reaction is not specified, it was conducted at room temperature. Preparative chromatographic separations were performed on silica gel (Merck 60) columns, with the eluents given in brackets and monitoring of the effluent by thin-layer chromatography on silica gel plates. Spots were visualized by ultraviolet light or by spraying with 10% H_2SO_4 in EtOH. Melting points were measured on a Reichert hot stage apparatus and are uncorrected. Optical rotations were measured at 20 °C with a Roussel-Jouan electronic digital micropolarimeter. Proton NMR spectra were recorded at 250 MHz with a Bruker Model AM 250 spectrometer, at 400 MHz with a spectrometer constructed in this university, or at 90 MHz with a Perkin-Elmer Model R-32 spectrometer. NMR chemical shifts are expressed in parts per million downfield from

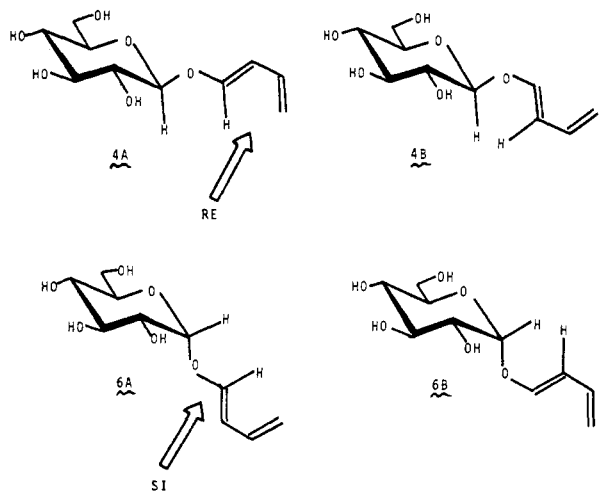
(23) Brewster, J. H. *J. Am. Chem. Soc.* **1959**, *81*, 5483.
(24) Smith, W. B. *J. Org. Chem.* **1979**, *44*, 1631. Chen, S.; Watson, W. H. *Cryst. Struct. Commun.* **1980**, *9*, 57.
(25) David, S.; Lubineau, A.; Thieffry, A. *Tetrahedron* **1978**, *34*, 279.

Scheme VI[a]

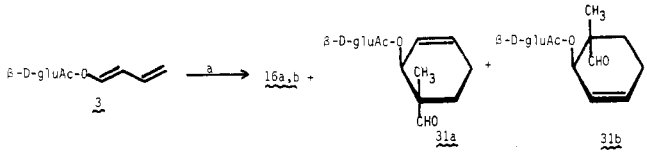


[a] (a) CH_2=$CH(CH_3)CHO$, H_2O, 20 °C, 6 h; (b) Ac_2O, pyridine, 20 °C, 24 h; (c) H_2, Pd/C, EtOH–AcOEt, 1:1, 20 °C, 5 h; (d) $NaBH_4$, H_2O, 0 °C, 2 h; (e) H_2SO_4, 1 N, 100 °C, 18 h or α-glucosidase, H_2O, 37 °C; 14 days.

Scheme VII



Scheme VIII[a]



[a] (a) CH_2=$CH(CH_3)CHO$, toluene, 80 °C, 7 days.

internal tetramethylsilane. Coupling constants (J) are given in hertz with splitting patterns designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Elemental analyses were performed by the Service Central de Microanalyse du CNRS. The glucosidases were purchased from Sigma.

Preparation of Aldehyde 2. The sodium salt of malonaldehyde[19] (9.4 g, 100 mmol) was added to a stirred solution of acetobromoglucose (20.5 g, 50 mmol) in dry Me_2SO (100 mL). After 4 h, the mixture was poured into ether (2 L), and the resultant suspension was cooled to 0 °C. After decantation, the precipitate was dissolved in a mixture of CH_2Cl_2 and water. The organic layer was washed with water, dried (Na_2SO_4), filtered, and evaporated. Additional crude aldehyde could be obtained from the ether–Me_2SO mixture; evaporation of the ether gave an oil which was diluted with CH_2Cl_2, thoroughly washed with water to remove most of the Me_2SO, dried (Na_2SO_4), filtered, and evaporated. The aldehyde **2** (11.3 g, 56%) was obtained as white crystals from a solution of the mixed residues dissolved in the minimum of CH_2Cl_2 and diluted with ether and a small quantity of hexane: mp 134.5–135 °C, $[\alpha]^{20}_D$ −22° (c 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.02, 2.04, 2.06, and 2.08 (4 s, 12 H), 3.86 (ddd, J = 2, 5, 10 Hz, 1 H), 4.13 (dd, J = 13, 2 Hz, 1 H), 4.26 (dd, J = 13, 5 Hz, 1 H), 5.03 (d, J = 7 Hz, 1 H), 5.14 (t, J = 10 Hz, 1 H), 5.19 (t, J = 7 Hz, 1 H), 5.26 (t, J = 10 Hz, 1 H), 5.77 (dd, J = 13, 8 Hz, 1 H), 7.31 (d, J = 13 Hz, 1 H), 9.41 (d, J = 8 Hz, 1 H). Anal. Calcd for $C_{17}H_{22}O_{11}$: C, 50.75; H, 5.47; O, 43.78. Found: C, 50.45; H, 5.62; O, 43.57.

Preparation of Diene 3. To a cold (−78 °C) solution of aldehyde **2** (8.5 g, 21 mmol) in dry THF (200 mL) was added a salt-free solution of triphenylmethylenephosphorane in toluene (0.78 M, 40 mL) dropwise over 30 min. The red solution was warmed to −20 °C and poured into a mixture of CH_2Cl_2 and phosphate buffer (pH 7). After separation, the organic layer was washed with water, filtered through a 2-in. plug of Florisil, and evaporated. Chromatography (CH_2Cl_2–ether–hexane, 1:1:2) gave the crystalline diene **3** (7.05 g, 83%): mp 152–153 °C; $[\alpha]^{20}_D$ −13.3° (c 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.02, 2.03, 2.05, and 2.09 (4 s, 12 H), 3.76 (ddd, J = 10, 5, 2 Hz, 1 H), 4.12 (dd, J = 12, 2 Hz, 1 H), 4.26 (dd, J = 12, 5 Hz, 1 H), 4.77 (d, J = 8 Hz, 1 H), 4.93 (d, J = 10.5 Hz, 1 H), 5.06 (d, J = 17 Hz, 1 H), 5.10 (dd, J = 9, 8 Hz, 1 H), 5.12 (t, J = 9 Hz, 1 H), 5.23 (t, J = 9 Hz, 1 H), 5.80 (dd, J = 12, 10.5 Hz, 1 H), 6.16 (dt, J = 17, 10.5 Hz, 1 H), 6.50 (d, J = 12 Hz, 1 H). Anal. Calcd for $C_{18}H_{24}O_{10}$: C, 53.99; H, 6.04; O, 39.96. Found: C, 54.09; H, 6.21; O, 39.85.

Preparation of Diene 5. Following the above procedure, except that the salt-free solution of triphenylmethylenephosphorane in toluene (0.78 M, 23 mL) was added dropwise to a stirred solution of aldehyde **2** (6.03 g, 15 mmol) at room temperature. After 35 min, workup as above yielded a mixture of dienes **3** and **5**, which were separated by chromatography (CH_2Cl_2–Et_2O–hexane, 1:1:2) to give in order of elution the diene **5** (3.21 g, 54%) followed by the diene **3** (1.07 g, 18%). Diene **5**: mp 76.5–77 °C; $[\alpha]^{20}_D$ +154° (c 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.01, 2.02, 2.06, and 2.065 (4 s, 12 H), 3.98 (ddd, J = 10, 5, 2 Hz, 1 H), 4.08 (dd, J = 12, 2 Hz, 1 H), 4.22 (dd, J = 12, 5 Hz, 1 H), 4.93 (m, 2 H), 5.08 (m, 2 H), 5.35 (d, J = 3.5 Hz, 1 H), 5.51 (t, J = 10 Hz, 1 H), 5.90 (dd, J = 12, 10 Hz, 1 H), 6.16 (dt, J = 17, 10 Hz, 1 H), 6.46 (d, J = 12 Hz, 1 H). Anal. Calcd for $C_{18}H_{24}O_{10}$: C, 53.99; H, 6.04; O, 39.96. Found: C, 54.08; H, 6.08; O, 39.88.

General Procedure for Ester Hydrolysis of Peracetylated Dienes 3 and 5. A solution of peracetylated diene (4 g, 10 mmol) in a mixture of MeOH–NEt_3–H_2O (8:1:1, 100 mL) was stirred overnight at room temperature. The resultant clear solution was

then coevaporated under vacuum several times with water until the odorless solid residue (free from triethylammonium salts) reached a constant weight. The crude water-soluble dienes **4** or **6** obtained in a quantitative yield were then used in cycloaddition without further purification.

Aqueous Cycloaddition of Diene 4 with Acrolein. Preparation of Peracetylated Adducts 9a,b. Freshly distilled acrolein (3.4 mL, 40 mmol) was added to a solution of diene **4** (2.32 g, 10 mmol) in water (20 mL). After 3 h, the reaction mixture was evaporated. Sodium borohydride (0.378 g) was then added portionwise to a cold (0 °C) solution of the residue in phosphate buffer (pH 7, 30 mL). After 0.5 h, the mixture was quenched by careful addition of acetic acid and evaporated. Chromatography (MeOH–EtOAc, 1:1) of the residue gave a mixture of **8a,b** which was dissolved in pyridine (50 mL) and treated with acetic anhydride (10 mL). After 24 h, the reaction mixture was coevaporated several times with toluene to give a mixture of **9a,b** (4.6 g, 92%), from which the pure major stereoisomer **9a** was obtained by fractional crystallization (ether–hexane) **9a**: mp 109–110 °C; $[\alpha]^{20}_D$ +107.8° (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.52 (m, 2 H), 1.90–2.26 (m, 18 H), 3.71 (ddd, J = 10, 5, 2 Hz, 1 H), 3.96 (dd, J = 10.5, 8 Hz, 1 H), 4.00 (m, 2 H), 4.15 (dd, J = 11, 5 Hz, 1 H), 4.25 (dd, J = 11, 5 Hz, 1 H), 4.60 (d, J = 7.5 Hz, 1 H), 5.01 (dd, J = 9, 7.5 Hz, 1 H), 5.05 (t, J = 9 Hz, 1 H), 5.19 (t, J = 9 Hz, 1 H), 5.81–5.98 (m, 2 H). Anal. Calcd for $C_{23}H_{32}O_{12}$: C, 55.19; H, 6.44; O, 38.36. Found: C, 55.39; H, 6.45; O, 37.70.

Stereochemical Course of the Cycloaddition of the Diene 4 with Acrolein. Preparation of Saturated Adducts 10a,b. To a solution of the crude mixture **8a,b** (2.6 g, 9 mmol) in a mixture of methanol–ethyl acetate (65:35, 100 mL) was added 10% palladium on carbon (0.4 g), and after evacuation and purging with H_2, the mixture was stirred for 5 h under H_2. Filtration through Celite and evaporation followed by silica gel chromatography (AcOEt–2-propanol–water, 17:2:1) afforded saturated compounds **10a,b**.

Removal of the Glucose Moiety. Preparation of *cis*-2-(Hydroxymethyl)cyclohexanol (11a,b). Acidic Hydrolysis (Method A). A solution of **10a,b** (0.509 g, 1.74 mmol) in sulfuric acid (1 N, 20 mL) was heated at 100 °C. After 17 h, the reaction mixture was quenched with aqueous potassium bicarbonate (10%) and extracted with CH_2Cl_2 (7 × 30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated. Silica gel chromatography (AcOEt) gave *cis*-2-(hydroxymethyl)cyclohexanol (**11a,b**) (70 mg, 31%) in a ratio of 58:42 as determined by optical rotation measurements, $[\alpha]^{20}_D$ +5.74 (*c* 0.62, H_2O) [lit.[21] $[\alpha]^{25}_D$ −36.0° (*c* 0.42, H_2O), for the (1*R*,2*R*)-2-(hydroxymethyl)cyclohexanol (**11a**)]: ^1H NMR (D_2O, 250 MHz) δ 1.15–1.89 (m, 9 H), 3.50 (dd, J = 11, 7 Hz, 1 H), 3.63 (dd, J = 11, 7 Hz, 1 H), 4.05 (m, 1 H). The chromatographic and spectroscopic properties of **11a,b** were identical in every respect with an authentic sample prepared as in ref 22. The route given in this reference was slightly modified: *cis*- and *trans*-2-(methoxycarbonyl)cyclohexanol were separated by silica gel chromatography (ether–hexane, 1:3) before $LiAlH_4$ reduction to give separately pure *cis*- and *trans*-2-(hydroxymethyl)cyclohexanol. All spectroscopic data were in agreement with those reported in ref 21 for both stereoisomers.

Enzymatic Hydrolysis (Method B). β-Glucosidase (180 mg, 900 units) was added to a solution of **10a,b** (730 mg, 2.5 mmol) in twice-distilled water (40 mL). After 3.5 days at 37 °C, the reaction mixture was extracted with EtOAc (6 × 30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated. Silica gel chromatography (AcOEt) gave *cis*-2-(hydroxymethyl)cyclohexanol (**11a,b**) (200 mg, 62%) identical with the above sample.

Aqueous Cycloaddition of Diene 4 with Methyl Acrylate. Preparation of 12a,b. Freshly distilled methyl acrylate (1.63 mL, 18 mmol) was added to a solution of diene **4** (0.842 g, 3.62 mmol) in water (7.2 mL). After 18.5 h at 60 °C, the reaction mixture was evaporated. Silica gel chromatography (AcOEt–MeOH, 9:1) afforded **12a,b** (0.763 g, 66%) from which the pure major diastereoisomer **12a** was obtained by fractional crystallization (acetone). **12a**: mp 75–85 °C; $[\alpha]^{20}_D$ +136° (*c* 0.5, H_2O); ^1H NMR (CD_3OD, 250 MHz) δ 1.80–2.50 (m, 4 H), 2.68 (dt, J = 11.5, 4 Hz, 1 H), 3.10 (dd, J = 9, 8 Hz, 1 H), 3.23–3.35 (m, 3 H, and CD_3OD impurities), 3.65 (m, 1 H), 3.72 (s, 3 H), 3.87 (dd, J = 12, 2.5 Hz, 1 H), 4.33 (d, J = 7.5 Hz, 1 H), 4.40 (br t, J = 9 Hz, 1 H), 5.85–6.02 (m, 2 H).

Stereochemical Course of the Cycloaddition of Diene 4 with Methyl Acrylate. Preparation of the Saturated Adducts 14a,b. To a solution of **12a,b** (2.54 g, 8 mmol) in a mixture of ethanol–ethyl acetate (2:1, 80 mL), 10% Pd/C (0.36 g) was added, and after evacuation and purging with H_2, the mixture was stirred for 6.5 h under H_2. Filtration through Celite and evaporation followed by silica gel chromatography (AcOEt–MeOH, 9:1) gave **13a,b** (2.3 g, 90%).

Enzymatic Hydrolysis of 13a,b. Preparation of *cis*-2-(Methoxycarbonyl)cyclohexanol (14a,b). β-Glucosidase (260 mg, 1670 units) was added to a solution of **13a,b** (1.439 g, 4.5 mmol) in phosphate buffer (pH 5, 100 mL). After 7 days at 37 °C, the reaction mixture was extracted with AcOEt (3 × 30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated. Kugelrohr distillation gave **14a,b** as a colorless oil (516 mg, 72.5%, 130–132 °C (25 mm)) in a ratio of 2.5:1 as determined by optical rotation measurements: $[\alpha]^{20}_D$ +15.1° (*c* 4.7, Et_2O) [lit.[22] $[\alpha]_D$ +31.7° (*c* 4.2, Et_2O) for the (1*S*,2*R*)-2-(methoxycarbonyl)cyclohexanol (**14a**)]; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.15–1.90 (m, 8 H), 2.43 (ddd, J = 10.5, 3.5, 2 Hz, 1 H), 3.35 (br s, 1 OH), 3.66 (s, 3 H), 4.10 (m, 1 H). A solution of **14a,b** (120 mg) in ether (5 mL) was added dropwise to a cold (0 °C) suspension of $LiAlH_4$ (50 mg) in ether (20 mL). After 15 min at 0 °C, water was added, and the organic solution was decanted and evaporated. Silica gel chromatography (EtOAc) gave **11a,b** (80 mg, 82%) identical in every respect with **11a,b** obtained from the cycloaddition of diene **4** with acrolein and with an authentic sample prepared as in ref 22 (vide supra).

Aqueous Cycloaddition of Diene 4 with Methacrolein. Preparation of 16a,b. Freshly distilled methacrolein (0.75 mL, 9.1 mmol) was added to a solution of diene **4** (0.645 mg, 2.78 mmol) in water (6 mL). After 3.5 h, the reaction mixture was evaporated. The residue was dissolved in pyridine (10 mL) and treated with acetic anhydride (2.1 mL). After 24 h, the reaction mixture was coevaporated several times with toluene. Silica gel chromatography (hexane–ethyl acetate, 7:3) gave **16a,b** (1.18 g, 90%) in a ratio of 60:40 as determined by ^1H NMR ($CDCl_3$, 400 MHz). The pure stereoisomer **16a** could be obtained by fractional crystallization (ether). **16a**: mp 151 °C; $[\alpha]^{20}_D$ +77° (*c* 0.8, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.04 (s, 3 H), 1.49–2.15 (m, 16 H), 3.70 (ddd, J = 10, 5, 2 Hz, 1 H), 4.00 (br s, 1 H), 4.15 (dd, J = 12, 2 Hz, 1 H), 4.23 (dd, J = 12, 5 Hz, 1 H), 4.60 (d, J = 8 Hz, 1 H), 4.98 (dd, J = 10.5, 8 Hz, 1 H), 5.03 (t, J = 10.5 Hz, 1 H), 5.17 (t, J = 10.5 Hz, 1 H), 5.88 (br s, 2 H), 9.60 (s, 1 H). Anal. Calcd for $C_{22}H_{30}O_{11}$: C, 56.16; H, 6.43; O, 37.41. Found: C, 56.07; H, 6.53; O, 37.48.

Stereochemical Course of the Cycloaddition of Diene 4 with Methacrolein. Preparation of 17a,b. To a solution of crude **15a,b** (2.8 g, 9.3 mmol) in a mixture of EtOH–EtOAc (2:1, 90 mL), 10% Pd/C (0.35 g) was added, and after evacuation and purging with H_2, the mixture was stirred for 24 h under H_2; filtration through Celite and evaporation gave a crude mixture of **17a,b**.

Preparation of Diols 19a,b. Sodium borohydride (0.19 g, 5 mmol) was added portionwise to a cold (5 °C) solution of crude **17a,b** (1.52 g, 5 mmol) in water (20 mL). After 2 h at 5 °C, the reaction was quenched by careful addition of AcOH. The reaction mixture was then coevaporated several times with MeOH. Silica gel chromatography (MeOH–EtOAc, 1:9) afforded **18a,b** (1.50 g) which were directly hydrolyzed either under acidic or enzymatic conditions.

Acidic Hydrolysis (Method A). A solution of the above mixture **18a,b** (0.596 g, 1.94 mmol) in sulfuric acid (1 N, 6 mL) was heated at 100 °C. After 18.5 h, the reaction was quenched with aqueous potassium bicarbonate (10%), and the reaction mixture was extracted with ethyl acetate (6 × 20 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated. Silica gel chromatography (ether–hexane, 2:1) provided 0.182 g (65%) of diols **19a,b** in a ratio of 1.5:1 as judged by ^1H NMR ($CDCl_3$, 90 MHz) examination with 20% Eu $(hfc)_3$ shift reagent and optical rotation measurement: $[\alpha]^{20}_D$ +3° (*c* 1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.01 (s, 3 H), 1.04–1.8 (m, 8 H), 3.4 (dd, J = 10.5, 5.5 Hz, 1 H), 3.60 (m, 1 H), 3.68 (d, J = 5 Hz, 1 H), 3.78 (t, J = 5.5 Hz, 1 H), 3.83 (dd, J = 10.5, 5.5

Hz); ^{1}H NMR ($CDCl_3$, D_2O, 250 MHz) δ 1.00 (s, 3 H), 1.04–1.8 (m, 8 H), 3.4 (d, J = 10.5 Hz, 1 H), 3.60 (dd, J = 9, 2.5 Hz, 1 H), 3.88 (d, J = 10.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.25, 22.46, 22.64, 30.67, 32.40, 38.32, 70.09, and 77.24. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18; O, 22.19. Found: C, 66.67; H, 11.21; O, 22.01.

Enzymatic Hydrolysis (Method B). β-Glucosidase (50 mg 250 units) was added to a solution of **18a,b** (0.411 g, 1.34 mmol) in twice-distilled water (50 mL). After 24 h at 37 °C, the reaction mixture was extracted with ethyl acetate (6 × 30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated to yield 0.15 g (78%) of the diols **19a,b** identical in every respect with the above mixture.

Preparation of (1*S*,2*R*)-2-Formyl-2-methylcyclohexyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (20a). To a solution of **16a** (0.339 g, 0.7 mmol) in ethyl acetate (25 mL) was added 10% Pd/C (50 mg), and after evacuation and purging with H_2, the mixture was stirred for 5 h under H_2. Then, filtration through Celite and evaporation gave **20a** (0.540 g, 100%) as white crystals: mp 133–134 °C (ether–hexane); $[\alpha]^{20}_D$ −4° (c 1, CH_2Cl_2). Anal. Calcd for $C_{22}H_{32}O_{11}$: C, 55.92; H, 6.83; O, 37.25. Found: C, 56.02; H, 6.85; O, 37.19.

Preparation of (1*S*,2*S*)-2-(Hydroxymethyl)-2-methylcyclohexyl 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranoside (21a). Sodium borohydride (50 mg, 1.32 mmol) was added portionwise to a solution of **20a** (0.352 g, 0.74 mmol) in ethanol (20 mL). After 5 min at room temperature, the reaction was quenched by careful addition of AcOH. After several coevaporations with MeOH, silica gel chromatography (Et_2O–CH_2Cl_2, 1:1) of the residue gave **21a** (315 mg, 90%) as white crystals: mp 138–139 °C (Et_2O–hexane); $[\alpha]^{20}_D$ −5.8° (c 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.03 (s, 3 H), 1.04–1.97 (m, 8 H), 2.02 (s, 3 H), 2.05 (s, 3 H), 2.1 (s, 6 H), 3.23 (br d, J = 11 Hz, 1 H), 3.49 (dd, J = 8, 4 Hz, 1 H), 3.70 (ddd, J = 10, 5.5, 2.5 Hz, 1 H), 3.83 (d, J = 11 Hz, 1 H), 4.11 (dd, J = 12, 2.5 Hz, 1 H), 4.26 (dd, J = 12, 5.5 Hz, 1 H), 4.58 (d, J = 8 Hz, 1 H), 5.00 (dd, J = 10, 8 Hz, 1 H), 5.05 (t, J = 10 Hz, 1 H), 5.20 (t, J = 10 Hz, 1 H). Anal. Calcd for $C_{22}H_{34}O_{11}$: C, 55.69; H, 7.22; O, 37.09. Found: C, 55.90; H, 7.16; O, 37.19.

(1*S*,2*S*)-2-(Hydroxymethyl)-2-methylcyclohexanol (19a). A solution of **21a** (0.206 g, 0.43 mmol) in sulfuric acid (1 N, 10 mL) was heated at 100 °C. After 4 h, the reaction was quenched with aqueous potassium bicarbonate (10%). The reaction mixture was then extracted with EtOAc (6 × 30 mL). The combined organic layers were dried, filtered, and evaporated. Silica gel chromatography (Et_2O–hexane, 2:1) gave **19a** (41 mg, 66%) as white crystals: mp 61.5 °C (EtOAc–hexane); $[\alpha]^{20}_D$ +15° (c 0.6, CH_2Cl_2); the ^{1}H NMR ($CDCl_3$, 250 MHz) was identical with the enantiomeric mixture **19a,b** as described above. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18; O, 22.19. Found: C, 66.18; H, 10.76; O, 22.27.

Aqueous Cycloaddition of Diene 6 with Methacrolein. Freshly distilled methacrolein (0.95 mL, 11.5 mmol) was added to a solution of diene **6** (0.534 g, 2.3 mmol) in water (5 mL). After 6 h, the reaction mixture was evaporated to give a crude mixture of **22a,b** and **23a,b**. The residue was then dissolved in dry pyridine (10 mL) and treated with acetic anhydride (1.75 mL). After 24 h, the reaction mixture was coevaporated several times with toluene. Silica gel chromatography (hexane–EtOAc, 7:3) gave a mixture of *endo*-**24a,b** and *exo*-**25a,b** stereoisomers (0.843 g, 78%). ^{1}H NMR ($CDCl_3$, 250 MHz) showed a 15.8:27:1:2.2 ratio of **24a**/**24b**/**25a**/**25b**, using aldehyde and methyl signals: CHO δ 9.44 (2.22), 9.51 (1), 9.61 (27), 9.73 (15.8); CH_3 δ 1.00 (27), 1.07 (15.8), 1.16 (2.2), 1.18 (1). Anal. Calcd for $C_{22}H_{30}O_{11}$: C, 56.16; H, 6.43; O, 37.41. Found: C, 55.29; H, 6.41; O, 37.20.

Stereochemical Course of the Aqueous Cycloaddition of Diene 6 with Methacrolein. Preparation of Saturated Adducts 26a,b and 27a,b. A mixture of stereoisomers **22a,b** and **23a,b** (1.8 g, 6 mmol) was dissolved in EtOH–EtOAc (1:1, 80 mL). Pd/C (10%) (0.25 g) was added, and after evacuation and purging with H_2, the mixture was stirred for 5 h under H_2. Filtration through Celite and evaporation afforded **26a,b** and **27a,b** (1.8 g, 100%).

Preparation of Polyols 28a,b and 29a,b. Sodium borohydride (0.195 g, 5.12 mmol) was added portionwise to a cold (0 °C) solution of **26a,b** and **27a,b** (1.56 g, 5.12 mmol) in water 20 mL. After 2 h at 0 °C, the reaction was quenched by careful addition of AcOH, and the reaction mixture was coevaporated several times with MeOH. Silica gel chromatography (EtOAc–MeOH, 9:1) gave the polyols **28a,b** and **29a,b** (1.5 g, 96%).

Preparation of Diols 19a,b and 30a,b. Acidic Hydrolysis (Method A). A solution of the above mixture **28a,b** and **29a,b** (0.59 g, 1.9 mmol) in sulfuric acid (1 N, 10 mL) was heated at 100 °C. After 18 h, the reaction was quenched with aqueous potassium bicarbonate (10%) and the reaction mixture extracted with ethyl acetate (6 × 30 mL). The combined organic layers were washed with brine, dried, filtered, and evaporated. Silica gel chromatography (ether–hexane, 2:1) gave the diols **19a,b** and **30a,b** (0.188 g, 68%). ^{1}H NMR ($CDCl_3$, 250 MHz) showed a 13.2:1 ratio of **19a,b**/**30a,b** using the methyl signals: CH_3 δ 0.96 (1), 1.00 (13.2). In addition to the signals reported above for **19a,b**, the following signals were assigned to **30a,b**: ^{1}H NMR ($CDCl_3$) δ 0.96 (s, 3 H), 1.12–1.82 (m, 9 H), 3.22 (br s, 2 OH), 3.39 (d, J = 13 Hz, 1 H), 3.48 (d, J = 13 Hz, 1 H), 3.60 (dd, J = 15, 6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 13.57, 20.60, 24.72, 30.39, 33.53, 39.33, 74.80, 77.11. Rough separation of the mixture using silica gel chromatography (ether–hexane, 1:1) gave pure **19a,b** along with a mixture of **19a,b** and **30a,b**. **19a,b**: $[\alpha]^{20}_D$ −5° (c 1.1, CH_2Cl_2) which confirmed the 36:64 ratio of **19a**/**19b**.

Enzymatic Hydrolysis (Method B). α-Glucosidase (50 mg, 150 units) was added to a solution of the mixture **29a,b** and **30a,b** (0.459 g, 1.5 mmol) in twice-distilled water (50 mL). After 1 week at 37 °C, a new batch of α-glucosidase (50 mg, 150 units) was added. After 1 week more at 37 °C, the reaction mixture was extracted with ethyl acetate (6 × 30 mL). The combined organic layers were dried, filtered, and evaporated to yield the same mixture of **19a,b**/**30a,b** (0.160 g, 74%) as above.

Stereochemical Course of the Cycloaddition of Diene 5 with Methacrolein in Toluene. Preparation of Adducts 24a,b and 25a,b. Freshly distilled methacrolein (0.7 mL, 8.4 mmol) was added to a solution of diene **5** (0.674 g, 1.68 mmol) in toluene (5 mL) (containing few crystals of hydroquinone). After 1 week at 80 °C, the reaction mixture was evaporated. Chromatography (hexane–EtOAc, 7:3) gave a mixture of *endo*-**24a,b** and *exo*-**25a,b** stereoisomers (0.748 g, 94%). ^{1}H NMR ($CDCl_3$, 250 MHz) showed a 7.5:13.3:1:2.6 ratio of **24a**/**24b**/**25a**/**25b** using aldehyde and methyl signals as above.

Stereochemical Course of the Cycloaddition of Diene 3 with Methacrolein in Toluene. Freshly distilled methacrolein (0.83 mL, 10 mmol) was added to a solution of diene **3** (0.8 g, 2 mmol) in toluene (5 mL). After 1 week at 80 °C, the reaction mixture was evaporated. Chromatography (hexane–EtOAc, 7:3) gave a mixture of *endo*-**16a,b** and *exo*-**31a,b** stereoisomers (0.854 g, 91%). ^{1}H NMR ($CDCl_3$, 250 MHz) showed a 10.3:6.3:15:1 ratio of **16a**/**16b**/**31a**/**31b** using the methyl signals. In addition to the signals reported above for **16a,b**, the following signals were assigned to **31a,b**: CH_3 δ 1.07 (1.5), 1.13 (1); CHO δ 9.42 (1.5), 9.48 (1).

Acknowledgment. We thank Professor S. David for his interest and C.N.R.S. and University Paris-Sud for financial support.