Aqueous Cycloaddition using Glyco-organic Substrates. Facial Stereoselectivity in Diels–Alder Reactions of a Chiral Diene derived from D-Glyceraldehyde

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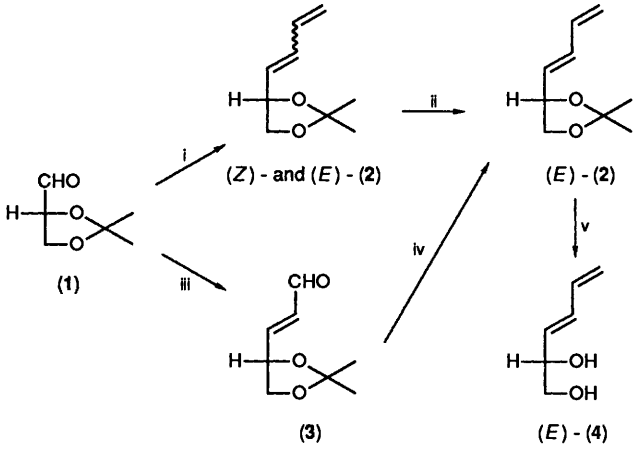
The preparation of a new chiral, water-soluble *E*-diene, which could be considered as the simplest diene obtainable from the simplest sugar, is described, along with its use in cycloaddition with acrylaldehyde. Water, as the solvent, enhanced the rate of the Diels–Alder reaction, promoted complete *regio*- and *endo*-selectivity, and improved a *like* (*anti*) facial selectivity,† compared with the results obtained with organic solvents.

As part of our programme for studying aqueous Diels–Alder reactions with glyco-organic substrates,[1] we decided to study the effect of water in the cycloaddition between acrylaldehyde and diene (**4**), which appears as the simplest carbohydrate-derived diene, derived from the simplest sugar, D-glyceraldehyde. We recently reported[1] a rate enhancement of Diels–Alder reactions in water upon using a butadienyl ether of glucose. The sugar moiety induced up to 82:18 facial stereoselectivity, which can be considered as a good result for thermal uncatalysed cycloadditions. Among the stereochemical features of the Diels–Alder reaction, facial differentiation of acyclic dienes having stereogenic allylic substituents is, at present, under much debate in the literature.[2–12] In this connection, we report herein a preparation of a water-soluble diene having such stereogenic allylic substituents, its cycloaddition with acrylaldehyde, and the complete assignment of the stereochemical course of the reaction.

Results

Preparation of Chiral Dienes.—Chiral dienes were prepared from 2,3-*O*-isopropylidene-D-glyceraldehyde (**1**) (see Scheme 1). The Wittig reaction[13] with the semi-stabilized allylidenetriphenylphosphorane gave diene (**2**) as a mixture of *E* and *Z* stereoisomers in the ratio 30:70, when the reaction was performed in tetrahydrofuran (THF) with BuLi as the base.

We recently studied[14] the selectivity of the Wittig reaction with allylic phosphoranes in order to help us prepare the pure *E*-isomer. The use of butyl ligand around the phosphorus atom was an alternative approach to this problem[15] In fact, when allylidenetributylphosphorane, generated from allyltributylphosphonium bromide and BuLi in THF, was allowed to react with aldehyde (**1**), the *E*-diene was obtained as the major product (isomeric ratio 69:31); when LiBr (1 mol equiv.) was added, *E*-selectivity increased, as expected,[16] to 87:13. Two other methods were investigated to ascertain whether or not they affected an increase in selectivity. First, the use of the commercial, but rather expensive, stabilized phosphorane $Ph_3P{=}CHCHO$ led to an almost pure *E*-stereoisomer (**3**);[17] a further Wittig reaction with methylenephosphorane generated *E*-diene (**2**) without affecting the stereochemical integrity of the first created double bond. Second, the 30:70 mixture of (*E*)- and (*Z*)-(**2**), resulting from the usual triphenylphosphorane, was isomerized with catalytic (0.01 mol equiv.) iodine under light. Isomerization was achieved after 1.5 h and gave (*E*)- and (*Z*)-(**2**) in the ratio 96:4, identical with that obtained in the two successive Wittig reactions. The same protected diene, as an 87:13 mixture of *E* and *Z* stereoisomers, was recently described,[18] as a by-product of a Mitsunobu reaction; however, the absolute configuration of this diene was incorrectly attributed. We must assign the (*S*)-configuration to this diene, since it is derived from D-glyceraldehyde. The hydrolysis of the acetal protecting group with Dowex 50 (H^+) resin afforded (*E*)- and (*Z*)-(**4**) in the ratio 96:4. Then, the almost pure *E*-dienes (**2**) and (**4**) were treated as chiral substrates in Diels–Alder reactions.



Scheme 1. *Reagents and conditions:* i, $Ph_3P{=}CHCH{=}CH_2$; ii, I_2 cat., hv; iii, $Ph_3P{=}CHCHO$; iv, $Ph_3P{=}CH_2$; v, H_3O^+.

Cycloaddition with Diene (**4**).—The Diels–Alder reaction of diene (**4**) with acrylaldehyde (see Scheme 2) was performed in

† Considering the diversity of the nomenclature which is used to define facial stereoselectivity in Diels–Alder reactions with chiral dienes having a stereogenic allylic substituent, it is necessary clearly to indicate our choice. In the depicted conformation (see Figure 1), which could not be the reactive one, *anti* addition refers to the *like* addition, following the Seebach–Prelog convention (D. Seebach and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **21**, 654).

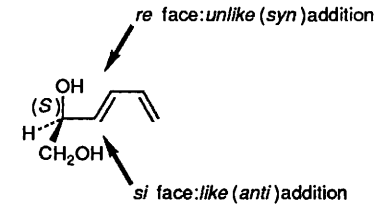


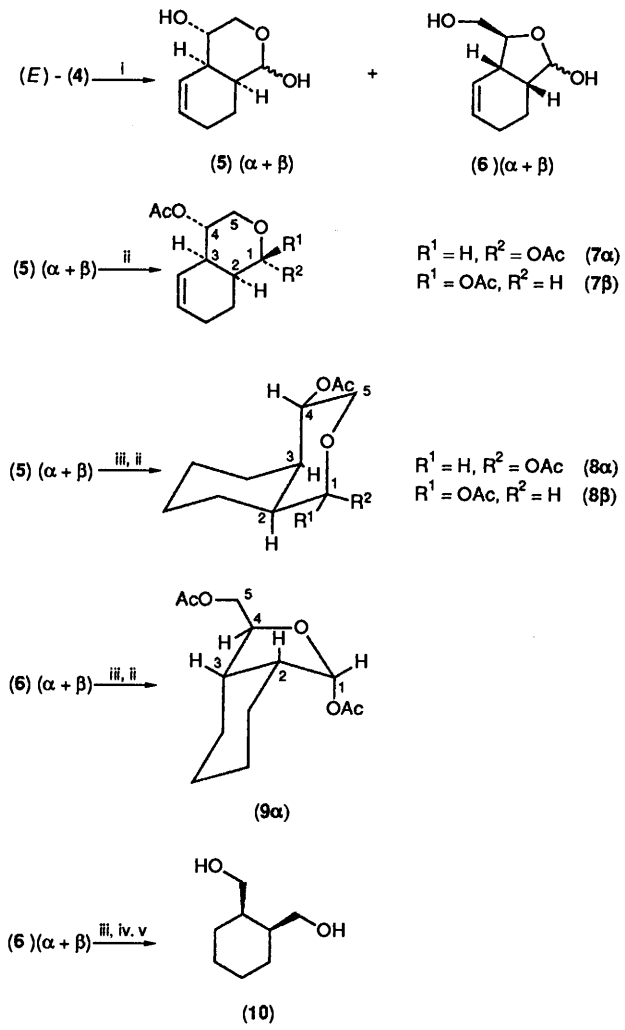
Figure 1. Facial selectivity in Diels–Alder reactions.

Table. Diels–Alder reaction between diene (**4**) and acrylaldehyde (10 mol equiv.).

Solvent	Conditions	Isolated yield	Stereofacial selectivity *endo si/endo re*
Toluene	4 days at 60 °C	94	55/45
Neat	2 days at 60 °C	73	55/45
Water	45 min at 90 °C	77	55/45
Water	2 h at 60 °C	77	65/35
Water	24 h at 20 °C	82	65/35
Water	7 days at 0 °C	92	66/34

water at room temperature; under these conditions, cycloaddition was complete within one day (82% isolated yield). ^{13}C NMR analysis of the mixture suggested the existence of 4-diastereoisomers in the proportions 43:22:32:3. As the cycloadducts could afterwards form hemiacetals, a third asymmetric carbon at the anomeric position was created during the course of the reaction. However, only two fractions, (**5**) and (**6**), in the ratio 2:1, could be isolated by preparative HPLC of the reaction product. The ^1H and ^{13}C NMR spectra of the major product (**5**) displayed two groups of signals δ_H 5.29 and 4.82, δ_C 101.51 and 94.88, which were particularly diagnostic of the presence of two anomers (α and β respectively). The fact that these two anomers (in the ratio 32:68) arose from a unique transition state was illustrated by a change in their composition during chemical manipulations in which anomerization could occur. Acetylation (Ac_2O, pyridine; 0 °C) of the mixture (**5**) (α + β) gave two separable anomers (**7α**) and (**7β**) in a ~50:50 ratio. The stereochemistry of these compounds was tentatively assigned as depicted in structures (**7α**) and (**7β**), based upon the coupling constants [$J_{1,2}$ < 1 Hz, $J_{3,4}$ 8.5 Hz in (**7α**), $J_{1,2}$ 4.3 Hz, $J_{3,4}$ 7.5 Hz in (**7β**)]. In order to prove this assignment, the mixture (**5**) (α + β) was hydrogenated (H_2, Pd/C), then acetylated (Ac_2O, pyridine; 0 °C) to give two separable anomers (**8α** and **8β**) in the ratio 96:4. The stereochemistry of those compounds, which is depicted conformationally in structures (**8α**) and (**8β**), respectively, was established by ^1H and ^{13}C NMR spectroscopy. The deshielding of 4-H (δ 5.17) *versus* 5-H and 5′-H (δ 3.87 and 3.61) and the chemical shifts of C-4 and C-5 (δ_C 65.74 and 62.66, respectively) in the major (96%) anomer (**8α**) were interpreted as being a consequence of formation of a pyranose ring.[19] All the coupling constants were determined in the major anomer (**8α**) ($J_{1,2}$ 2.5 Hz, $J_{2,3}$ 5 Hz, $J_{3,4}$ 9.5 Hz), which confirmed the stereochemistry as depicted. The coupling constants $J_{1,2}$ 3 Hz and $J_{3,4}$ 7.5 Hz in the ^1H NMR spectrum of the anomer (**8β**) confirmed our interpretation. All these experimental data led us to assign the major product (**5**) (α + β) as arising from the approach of the dienophile onto the *si* face of the diene through a pure *endo* transition state.

Similarly, the minor fraction (**6**) was a mixture of α and β anomers in the ratio 91:9, as indicated by its ^{13}C NMR spectrum which exhibited two signals in the anomeric region (δ_C 102.69 and 98.64, respectively). This mixture was hydrogenated (H_2, Pd/C), then acetylated (Ac_2O, pyridine; 0 °C) to give compound (**9**) as an anomerically pure α compound. The chemical shifts of C-4 and C-5 (δ_C 79.23 and 66.54, respectively) suggested a furanose ring,[19] as depicted. Besides, the protons 4-H, 5-H, and 5′-H gave a multiplet (ABC system) similar to that already observed in acetylated aldopentofuranoses.[20] The vicinal coupling constant $J_{2,3}$ 6 Hz indicated a *cis* relationship between the fused rings, which is a consequence of the *endo*



Scheme 2. *Reagents:* i, CH_2=CHCHO, water; ii, Ac_2O, Py; iii, H_2, Pd/C; iv, $NaIO_4$; v, $NaBH_4$.

transition state. In order to confirm this interpretation, the mixture (**6**) (α + β) was hydrogenated, cleaved with sodium periodate, then reduced with sodium borohydride to give the *meso* alcohol (**10**), devoid of optical activity.*

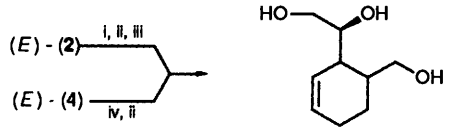
All these observations allowed us to ascertain that the minor compound (**6**) resulted from the *endo, re* transition state, whereas the major product (**5**) resulted from the *endo, si* transition state.

At this point, a question deserves some comment: why does the cycloadduct (**5**) adopt a pyranoid form, whereas (**6**) prefers the furanoid one? This result could be related to other observations in sugar chemistry. If we consider the oxygenated ring, compounds (**5**) and (**6**) correspond respectively to the configurations *lyxo* and *ribo*. It should be emphasized that lyxose exists exclusively in the pyranose form in aq. solution, whereas ribose partially adopts (24%) the furanose form under the same conditions.[22]

The cycloaddition was also investigated under several other conditions for the purposes of comparison, by modification of both the solvent and the reaction temperature. As can be seen in the Table, water as the solvent enhances both the rate and the stereofacial selectivity of the cycloaddition, but, unfortunately, the temperature in the range 0–60 °C, does not affect the facial selectivity in water. It must, however, be emphasized that the use of water allowed us to perform the cycloaddition at 0 °C with an excellent yield in a reasonable reaction time.

* The *threo*-diastereoisomer displays specific rotation $[\alpha]_D$ 22° (ref. 21).

Cycloaddition with Diene (**2**).—The Diels–Alder reaction of diene (**2**) with acrylaldehyde was performed in toluene at 60 °C, and yielded, after 6 days, an 88% yield of a mixture of 4 cycloadducts in the proportions 43:40:11:6, as indicated by ^{13}C NMR spectroscopy. Only two fractions could be separated by chromatography; however, NMR spectroscopic analysis of each of them was too complex for stereochemical assignment. We obviated this difficulty by converting the mixture into the triols (**11**) ($NaBH_4$ reduction at pH 7, to avoid epimerization, followed by hydrolysis of the dioxolane ring). In a parallel experiment the cycloadducts, resulting from the aq. Diels–Alder reaction with diene (**4**), were reduced to the same mixture of triols (**11**) (see Scheme 3).



(**11**)

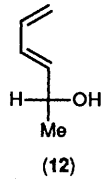
Scheme 3. *Reagents and conditions*: i, CH_2=CHCHO, PhMe; ii, $NaBH_4$; iii, H_3O^+; iv, CH_2=CHCHO, water.

A comparison of the two mixtures of triols (**11**), which come from either diene (**2**) in toluene or diene (**4**) in water, by analytical HPLC and ^{13}C NMR spectroscopy allowed us to assign the stereochemistry of the major cycloadducts (43%, *endo si* and 40%, *endo re*) obtained in toluene. The stereochemistry of the minor cycloadducts (11 and 6%) which probably arose from the *exo* transition state always present to some extent in the cycloaddition produced in organic solvents [1] was left undetermined.

Discussion

We, and others, have already shown that Diels–Alder reactions in water gave rise to considerable rate enhancement as a consequence of the hydrophobic effect.[1] Our new results confirm this general effect provided that the substrates used in the cycloaddition are water soluble. In this connection, diene (**4**), which could be considered as being derived from the simplest sugar, D-glyceraldehyde, with only two hydroxy groups, gave fair rate enhancements when compared with the reaction of diene (**2**) in toluene. Moreover, we observed complete regio- and *endo* selectivities, which is also typical for aq. cycloaddition.

More interestingly was the effect of water on facial stereochemistry. First of all, it must be noted that we observed a reverse facial selectivity in comparison with the cycloaddition of the similar diene (**12**) lacking the β-hydroxy group.[8]



(**12**)

Actually, we observed *anti* selectivity either with diene (**2**) in toluene or with diene (**4**) in toluene and water. Indeed the cycloaddition of diene (**2**) with acrylaldehyde in water led to unprotected cycloadducts, but it was impossible to know if the cycloaddition occurred on the protected or unprotected diene. Different models have been proposed to rationalize the relative topicity in cycloadditions using acyclic dienes with an allylic stereogenic centre. The perpendicular model, in which the heteroatom is perpendicular to the dienyl system, predicts *syn* selectivity by synperiplanar attack of the dienophile.[3,7] The coplanar model, in which the heteroatom lies in the plane outside the dienyl system, predicts [10] *syn* selectivity as well. Both of them failed to explain our *anti* selectivity without implication reaction of the β-hydroxy group. The similar behaviour of the two dienes (**2**) and (**4**) in toluene or under neat conditions could be related to their similar conformation, which should not differ in aprotic conditions, since an intramolecular hydrogen bond in diene (**4**) makes this diol look like the dioxolane ring in diene (**2**), and the *anti* selectivity could result from an attack from the less hindered side in the conformation depicted in Figure 2. Most striking is the influence of water in the selectivity of the reaction. Aq. cycloadditions between diene (**4**) and acrylaldehyde occur with an increased *anti* selectivity (*anti*:*syn* 2:1). As shown with *E*-substituted 1,3-dienes containing a centre of chirality at the allylic position,[7] the addition of dienophile will occur *syn* to the directing allylic functionality for groups having lone-pairs. In water, this lone-pair is involved in forming hydrogen bonds. Furthermore, it could be possible that the increase of *anti* selectivity implies a hydrophobic effect, which causes the dienophile to approach *anti* to the hydrophilic substituents, tightly bonded to water molecules.

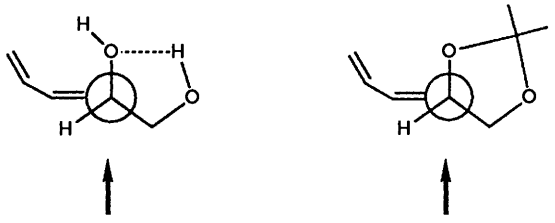


Figure 2. *anti*-Selectivity for dienes (**2**) and (**4**).

Experimental

(3Z)- *and* (3E)-(2S)-1,2-O-*Isopropylidenehexa*-3,5-*diene*-1,2-*diol* (**2**).—*Wittig reaction with allylidenetriphenylphosphorane.* To a suspension of allyltriphenylphosphonium bromide (25.22 g, 66 mmol) in THF (350 ml) was added at −40 °C a solution of butyl-lithium (1.6M, 66 mmol) in hexane. The mixture was allowed to warm to room temperature during 2 h, then was cooled to −78 °C before the addition of (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**1**) [23] (8.55 g, 66 mmol). After being allowed to warm to room temperature during 1 h, the reaction mixture was diluted with diethyl ether (1 1), washed with phosphate buffer (pH 7; 2 × 500 ml), dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (pentane–diethyl ether, 95:5 v/v) of the residue afforded an inseparable mixture (7.31 g, 72%) (70:30; ^1H NMR) of (3*Z*)- and (3*E*)-(2*S*)-1,2-*O*-isopropylidenehexa-3,5-diene-1,2-diol (**2**); δ($CDCl_3$; 250 MHz) 6.65 (0.7 H, dddd, *J* 16.5, 10.5, 10, and 1 Hz, CHC*H*=CH_2 for *Z* isomer), 6.42–6.25 (0.6 H, m, C*H*C*H*=CH_2 for *E* isomer), 6.18 (0.7 H, t, *J* 10.5 Hz, C*H*CH=CH_2 for *Z* isomer), 5.66 (0.3 H, ddd, *J* 14.5, 7.5, and 1 Hz, C*H*=CHCH=CH_2 for *E* isomer), 5.46 (0.7 H, dd, *J* 10.5 and 9 Hz, C*H*=CHCH=CH_2 for *Z* isomer), 5.29 (0.7 H, dd, *J* 16.5 and 1.5 Hz, =CH_2 for *Z* isomer), 5.25 (0.3 H, dd, *J* 15.5 and 1 Hz, =CH_2 for *E* isomer), 5.22 (0.7 H, dd, *J* 10 and 1.5 Hz, =CH_2 for Z isomer), 5.14 (0.3 H, dd, *J* 9.5 and 1 Hz, =CH_2 for *E* isomer), 4.99 (0.7 H, ddd, *J* 9, 8, and 6 Hz, OCH_2CHO for *Z* isomer), 4.54 (0.3 H, ddd, *J* 8, 7.5, and 6 Hz, OCH_2CHO for *E* isomer), 4.12 (0.7 H, dd, *J* 8 and 6 Hz, OCH_2CHO for *Z* isomer), 4.10 (0.3 H, dd, *J* 8 and 6 Hz, OCH_2CHO for *E* isomer), 3.60 (0.3 H, t, *J* 8 Hz, OCH_2CHO for *E* isomer), 3.56 (0.7 H, t, *J* 8 Hz, OCH_2CHO for *Z* isomer), and 1.41 and 1.46 (3 H, s, Me).

Isomerization of Diene (**2**).—Iodine (83 mg, 0.33 mmol) was

added to a 30:70 mixture of (*E*)- and (*Z*)-(**2**) (5.16 g, 33 mmol) in CH_2Cl_2 (66 ml). The solution was stirred under light at room temperature for 1.5 h. The rate of the isomerization was monitored by a change of colour from yellow to red. The reaction mixture was washed with saturated aq. sodium thiosulphate, dried over $MgSO_4$, and evaporated to yield (2S,3E)-1,2-O-*isopropylidenehexa*-3,5-*diene*-1,2-*diol* (4.86 g, 94%) as an oil; $[\alpha]_D^{20}$ +10° (*c* 1.04 in EtOH) (Found: C, 69.8; H, 8.9. $C_9H_{14}O_2$ requires C, 70.09; H, 9.15%). NMR analysis indicated 4% of the *Z*-isomer.

Wittig Reaction with Allylidenetributylphosphorane.—To a solution of allyltributylphosphonium bromide[24] (2.96 g, 9.16 mmol) in diethyl ether (73 ml) was added at −40 °C a solution of butyl-lithium (1.5M; 9.16 mmol) in hexane. The mixture was allowed to warm to room temperature and was then stirred for 2 h, then a solution of 2,3-*O*-isopropylideneglyceraldehyde (1.19 g, 9.16 mmol) in diethyl ether (18 ml) was added at room temperature. After 15 min, the reaction mixture was diluted with diethyl ether (50 ml), washed with phosphate buffer (3 × 150 ml), dried over $MgSO_4$, and concentrated under reduced pressure. Chromatography (pentane–diethyl ether, 95:5 v/v) gave a mixture of *E*- and *Z*-diene (**2**) (767 mg, 54%) in the ratio 69:31 (^{1}H NMR).

Sequence of two Wittig Reactions.—The aldehyde (**3**) (4.1 g, 26 mmol) obtained[17] from 2,3-*O*-isopropylideneglyceraldehyde and Ph_3P=CHCHO as a 96:4 mixture of *E* and *Z* isomers was dissolved in THF (260 ml). A solution of methylenetriphenylphosphorane (0.66M; 38 mmol) in toluene (58 ml) was then added dropwise at room temperature. The reaction mixture was stirred for 10 min, then poured into a mixture of phosphate buffer–dichloromethane (1:1 v/v). The organic layer was washed three times with water, filtered, dried, and evaporated. Chromatography of the residue afforded *E*-diene (**2**) (2.8 g, 70%) containing up to 4% of the *Z* isomer, according to NMR analysis.

(2S,3E)-*Hexa*-3,5-*diene*-1,2-*diol* (**4**).—Resin Dowex 50 (H^+) (3.2 g) was added to a solution of *E*-diene (**2**) (422 mg, 2.74 mmol) in a mixture of EtOH–water (9:1 v/v). After being stirred for 30 min at room temperature, the reaction mixture was filtered and evaporated. The *title compound* (**4**) was obtained as a syrup (contaminated with 4% of the *Z*-isomer); δ_H($CDCl_3$; 200 MHz) 6.32 (2 H, m, C*H*CH=CH_2), 5.68 (1 H, dd, *J* 14.5 and 6 Hz, C*H*=CHCH=CH_2), 5.25 (1 H, dd, *J* 16.5 and 1.5 Hz, CH=CH_2), 5.14 (1 H, dd, *J* 9 and 1.5 Hz, CH=CH_2), 4.3 (1 H, ddd, *J* 7.5, 6, and 3.5 Hz, C*H*OH), 3.68 (1 H, dd, *J* 11 and 3.5 Hz, CH_2OH), and 3.51 (1 H, dd, *J* 11 and 7.5 Hz, CH_2OH); δ_C($CDCl_3$; 50 MHz) 135.95, 131.91, and 131.76 (CHCH=CH), 117.29 (CH=CH_2), 72.21 (CHOH), and 65.78 (CH_2OH); $[\alpha]_D^{20}$ −43° (*c* 1.8 in EtOH) (Found: C, 62.55; H, 8.8. $C_6H_{10}O_2$ requires C, 63.14; H, 8.83%).

Cycloaddition between Diene (**4**) *and Acrylaldehyde in Water at Room Temperature.*—To a solution of diene (**4**) (1.67 g, 14.66 mmol) in twice distilled water (46 ml) was added acrylaldehyde (8.22 g, 146 mmol) previously distilled and stabilized with hydroquinone. A small amount of hydroquinone was then added and the mixture was stirred for 24 h under nitrogen. After evaporation of water, the residue was chromatographed (hexane–EtOAc, 50:50 v/v) to give the unreactive (2S,3Z)-*hexa*-3,5-*diene*-1,2-*diol* (70 mg, 4%); δ_H($CDCl_3$; 200 MHz) 6.65 (1 H, dtd, *J* 16.5, 11, and 1 Hz, CHC*H*=CH_2), 6.13 (1 H, t, *J* 11 Hz, C*H*CH=CH_2), 5.41 (1 H, dd, *J* 11 and 8.5 Hz, C*H*=CHCH=CH_2), 5.30 (1 H, dd, *J* 16.5 and 2 Hz, CH=CH_2), 5.22 (1 H, dd, *J* 11 and 2 Hz, CH=CH_2), 4.70 (1 H, tdd, *J* 8.5, 4, and 1 Hz, C*H*OH), 3.62 (1 H, dd, *J* 11 and 4 Hz, CH_2OH), and 3.51 (1 H, dd, *J* 11 and 8.5 Hz, CH_2OH); δ_C($CDCl_3$; 50 MHz) 131.56, 131.48, and 129.55 (CHCH=CH), 119.41 (CH=CH_2), 68.59 (CHOH), and 65.85 (CH_2OH); $[\alpha]_D^{20}$ −16° (*c* 1.14 in CH_2Cl_2 (Found: C, 63.2; H, 8.6. $C_6H_{10}O_2$ requires C, 63.14; H, 8.83%); the *major fraction* (**5**) (1.34 g, 54%); δ_H($CDCl_3$; 200 MHz) 5.8 and 5.6 (2 H, 2 m, CH=CH), 5.29 (0.32 H, d, *J* 2 Hz, 1-H for α anomer), 4.82 (0.68 H, d, *J* 6 Hz, 1-H for β anomer), 4.42 (1 H, td, *J* 7.5 and 4.5 Hz, 4-H), and 2.56 (1 H, br, 3-H); δ_C($CDCl_3$; 50 MHz) 129.57 and 122.86 (CH=CH for α anomer), 128.82 and 126.85 (CH=CH for β anomer), 101.51 and 94.88 (C-1 for α and β anomers, respectively), 80.51 and 69.21 (C-4 for α and β anomers, respectively), 65.66 and 64.32 (C-5 for β and α anomers, respectively), 44.30 and 37.58 (C-2 or C-3 for α anomer), 39.26 and 36.31 (C-2 or C-3 for β anomer), and 22.77, 22.30, 22.11, and 21.95 (CH_2CH_2 for α and β anomers); $[\alpha]_D^{20}$ −122° (*c* 1.13 in EtOH) (Found: C, 63.6; H, 8.0. $C_9H_{14}O_2$ requires C, 63.51; H, 8.29%); and the *minor fraction* (**6**) (0.67 g, 28%); δ_H($CDCl_3$; 200 MHz) 5.8 and 5.63 (2 H, 2 m, CH=CH), 5.2 (1 H, s, 1-H), 3.97 (1 H, ddd, *J* 8, 4, and 2 Hz, 4-H), 3.82 (1 H, dd, *J* 12 and 2 Hz, 5-H), 3.62 (1 H, dd, *J* 12 and 4 Hz, 5′-H), and 2.85 (1 H, m, 3-H); δ_C($CDCl_3$; 50 MHz) 128.23 and 124.80 (CH=CH for the major anomer), 127.85 and 127.63 (CH=CH for the minor one), 102.69 and 98.64 (C-1 for the major and minor anomers, respectively), 85.99 and 63.22 (C-4 and C-5), 44.73 and 36.02 (C-2 and C-3), and 23.37 and 21.87 (CH_2CH_2); $[\alpha]_D^{20}$ +45° (*c* 1 in CH_2Cl_2) (Found: C, 62.65; H, 8.6%).

Other Cycloadditions of Diene (**4**) *with Acrylaldehyde.*—The preceding experimental procedure is representative of all the cycloadditions between diene (**4**) and acrylaldehyde. Concentration of diene (**4**) in water or in toluene was 0.3M. After the end of the reaction (TLC), the reaction mixture was evaporated and the residue was analysed by ^{13}C NMR spectroscopy, to give the percentage of the cycloadducts (Table).

Preparation of Compounds (**7α**) *and* (**7β**).—A solution of the mixture of compounds (**5**) (α + β) (59 mg, 0.34 mmol) in a mixture of acetic anhydride (610 mg) and pyridine (360 mg) was kept overnight at 0 °C. After evaporation, chromatography (hexane–EtOAc, 85:15 v/v) of the residue afforded the two products (**7β**) (47 mg, 53%) and (**7β**) (41 mg, 46%).

Compound (**7β**): δ_H($CDCl_3$; 200 MHz) 5.85 (1 H, d, *J* 4.3 Hz, 1-H), 5.83 (1 H, ddt, *J* 10, 3.5, and 2 Hz, CHC*H*=CHCH$_2$), 5.65 (1 H, ddt, *J* 10, 4, and 2 Hz, CHCH=C*H*CH$_2$), 4.82 (1 H, td, *J* 7.5 and 4 Hz, 4-H), 3.82 (1 H, dd, *J* 11 and 4 Hz, 5-H), 3.69 (1 H, dd, *J* 11 and 7.5 Hz, 5′-H), 2.63 (1 H, m, 3-H), and 2.15 and 2.11 (6 H, s, Ac); $[\alpha]_D^{20}$ −78° (*c* 0.95 in CH_2Cl_2) (Found: C, 61.5; H, 7.15. $C_{13}H_{18}O_5$ requires C, 61.40; H, 7.14%).

Compound (**7α**): δ_H($CDCl_3$; 200 MHz) 6.1 (1 H, s, 1-H), 5.9 (1 H, m, CHC*H*=CHCH$_2$), 5.57 (1 H, ddt, *J* 10, 4, and 2 Hz, CHCH=C*H*CH$_2$), 4.51 (1 H, td, *J* 8.5 and 4 Hz, 4-H), 4.18 (1 H, dd, *J* 11.5 and 4 Hz, 5-H), 3.98 (1 H, dd, *J* 11.5 and 8.5 Hz, 5′-H), and 2.11 and 2.08 (6 H, s, Ac); $[\alpha]_D^{20}$ +16° (*c* 0.8 in CH_2Cl_2) (Found: C, 61.4; H, 7.2%).

Preparation of Compounds (**8α**) *and* (**8β**).—To a solution of compound (**5**) (α + β) (300 mg, 1.76 mmol) in EtOH (20 ml) was added 10% Pd/C (250 mg). The suspension was stirred under hydrogen at room temperature for 4 h, filtered through Celite, and concentrated under reduced pressure, then the residue was peracetylated as before. Flash chromatography (hexane–EtOAc, 65:35 v/v) gave compound (**8α**) (225 mg, 50%) and compound (**8β**) (9 mg, 2%).

Compound (**8α**): δ_H($CDCl_3$; 250 MHz) 5.79 (1 H, d, *J* 2.5 Hz, 1-H), 5.17 (1 H, td, *J* 9.5 and 5 Hz, 4-H), 3.87 (1 H, dd, *J* 11 and 5 Hz, 5-H), and 3.61 (1 H, dd, *J* 11 and 9.5 Hz, 5′-H); δ_H(C_6D_6; 200 MHz) 2.13 (1 H, dq, *J* 10 and 5 Hz, 3-H) and 1.66 and 1.62 (6 H, s, Ac); δ_C($CDCl_3$; 50 MHz) 94.35 (C-1), 65.74 (C-4), 62.66 (C-5), 39.21 (C-2), 34.25 (C-3), 25.11, 24.93, 24.72, and 21.14 ([CH_2]$_4$),

and 20.98 and 20.82 (*Me*CO); $[\alpha]_D^{20}$ +19° (*c* 0.9 in EtOH); m.p. 55 °C (Found: C, 60.9; H, 7.7. $C_{13}H_{20}O_5$ requires C, 60.92; H, 7.86%).

Compound (**8β**): δ_H($CDCl_3$; 250 MHz) 5.8 (1 H, d, *J* 3 Hz, 1-H), 5.02 (1 H, td, *J* 7.5 and 4 Hz, 4-H), 4.08 (1 H, dd, *J* 11.5 and 4 Hz, 5-H), 3.44 (1 H, dd, *J* 11.5 and 7.5 Hz, 5'-H), and 2.13 and 2.08 (6 H, s, Ac); $[\alpha]_D^{20}$ −38° (*c* 0.5 in EtOH); m.p. 75–78 °C.

Preparation of Compound (**9α**).—Following the same procedure for hydrogenation and acetylation, compounds (**6**) (α + β) (133 mg, 0.78 mmol) gave *compound* (**9α**) (102 mg, 51%); δ_H(C_6D_6; 250 MHz) 4.1 (4 H, m, 1- and 4-H, and 5-H_2), 2.05 (1 H, m, 3-H), 1.88 (1 H, dt, *J* 12 and 6 Hz, 2-H), 1.72 and 1.74 (6 H, s, Ac), and 1.3 and 1.0 (8 H, m, $[CH_2]_4$); irradiation at δ 1.3 gave $J_{2,3}$ 6 Hz and $J_{3,4}$ 9 Hz; δ_C($CDCl_3$; 50 MHz) 170.66 and 169.95 (Me*C*O), 102.38 (C-1), 79.23 (C-4), 66.54 (C-5), 43.94 and 35.92 (C-2 and -3), 24.29, 23.55, 22.98, and 20.87 ($[CH_2]_4$), and 21.17 and 20.65 (*Me*CO); $[\alpha]_D^{20}$ +4° (*c* 1 in CH_2Cl_2) (Found: C, 60.7; H, 7.6. $C_{13}H_{20}O_5$ requires C, 60.92; H, 7.86%).

Cycloaddition between Diene (**2**) *and Acrylaldehyde in Toluene.*—To a solution of diene (**2**) (300 mg, 1.94 mmol) in toluene (6.3 ml) was added freshly distilled acrylaldehyde (108 mg, 19.4 mmol), stabilized with hydroquinone. A small amount of hydroquinone was then added; the mixture was stirred at 60 °C under nitrogen for 6 days, then evaporated, and the residue was chromatographed to give, first the unreactive (*Z*)-diene, then the cycloadducts, which were collected as a unique fraction (378 mg, 88%) in the proportions 40:6:11:43; δ_C($CDCl_3$; 50 MHz) 204.42, 203.62, 203.60, and 202.76 (CHO). The mixture was dissolved in EtOH (2 ml) and the solution was added dropwise to a solution of $NaBH_4$ (128 mg) in EtOH–water (phosphate buffer, pH 7.8). The reaction mixture was stirred for 2.5 h. Acetone was then added in order to eliminate the excess of borohydride, and the mixture was extracted with EtOAc. After evaporation, the residue (343 mg) was dissolved in EtOH–water (9:1 v/v) and treated with resin Dowex 50 (H^+). The reaction mixture was stirred at room temperature for 5 h, then filtered and concentrated under reduced pressure. Flash chromatography (hexane–EtOAc, 50:50 v/v) gave *compound* (**11**) (155 mg, 50%) as a mixture of two triols; δ_C($CDCl_3$; 50 MHz) 129.60, 128.89, 125.88, and 124.72 (CH=CH), and 72.75 and 72.39 (CH_2OH); HPLC (Spherisorb C_{18}; 5 μ; diam. 4.6; 0.8 ml/min acetonitrile–water, 98:2 v/v) gave 2 peaks in the ratio 48:52 at t_R 8.58 and 9.35 min (Found: C, 62.6; H, 9.3. $C_9H_{16}O_3$ requires C, 62.76; H, 9.36%).

Comparison between Cycloaddition Selectivities in Toluene and in Water.—The cycloaddition between diene (**4**) and acrylaldehyde was performed as described above, but without purification. The residue (500 mg, 2.94 mmol) was added to a solution of $NaBH_4$ (333 mg, 8.82 mmol) in EtOH–water (phosphate buffer, pH 7). The reaction mixture was stirred at room temperature for 24 h; the excess of $NaBH_4$ was destroyed with acetone and the reaction mixture was extracted with EtOAc to afford a 65:35 mixture of *cis*-triols (**11**) (421 mg, 83%). The ^{13}C NMR spectrum and HPLC chromatogram were superposable with those resulting from cycloaddition between the diene and acrylaldehyde in toluene, except for the intensities of the NMR signals.

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