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Carbohydrate Research 270 (1995) 163–179

CARBOHYDRATE RESEARCH

# Preparation of $\alpha$- and $\beta$-dienyl glycosides used as dienes in aqueous Diels–Alder reactions. Influence of the carbohydrate moiety on the thermodynamics of the reaction

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Received 18 July 1994; accepted 30 November 1994

**Abstract**

A series of 1,3-butadienyl glycosides (mono- and di-saccharides) have been prepared and the kinetics of their Diels–Alder reaction with buten-2-one in water have been studied. The activation parameters for these aqueous cycloadditions provide clues for the hydration structure of such glyco-organic compounds.

*Keywords:* Organic synthesis in water; Cycloadditions; Dienyl glycosides; Kinetics; Sugar hydration

## 1. Introduction.

Studies directed towards the use of water as solvent for Diels–Alder reactions, have successively addressed the preparative [1], stereochemical [2] and physicochemical [3] aspects of the cycloaddition of butadienyl glucosides. The reactive part of these "glyco-organic" dienes is linked at the anomeric position of the sugar to permit facile removal of the solubilizing chiral inductor by either enzymic or acidic hydrolysis. To

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*SSDI* 0008-6215(95)00019-4

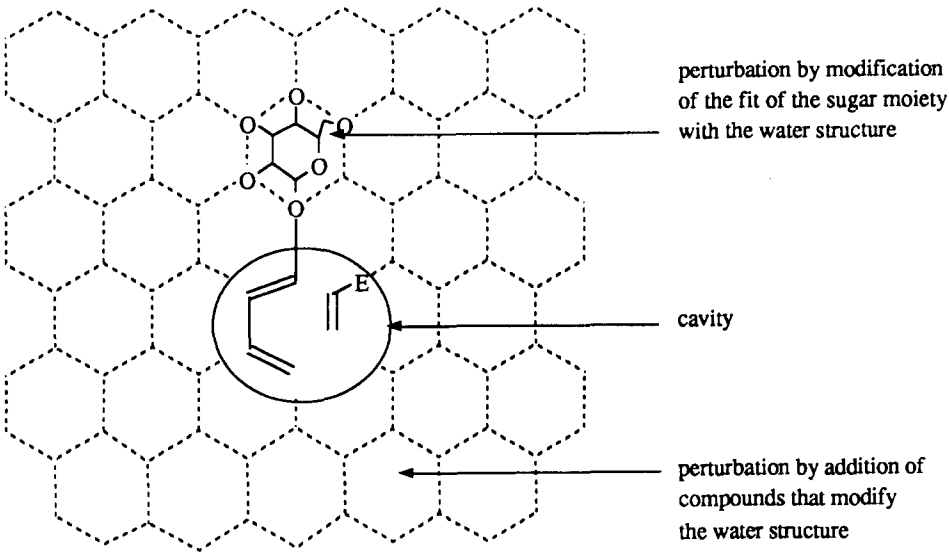



Fig. 1. Hypothesis for the microscopic structure of solvated glyco-organic dienes in water.

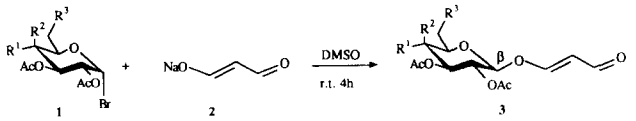
better understand the water – sugar interactions, we considered this reaction a chemical probe of the medium in studying the thermodynamics of the cycloaddition. Figure 1 depicts a model whereby the sugar fits into the water lattice-structure, whereas the diene part occupies a cavity. Two kinds of perturbations of the system may thereby be detected and analyzed by examining the kinetics and the activation parameters of the reaction.

The first aspect of this study has revealed the effect of such additives as glucose and sucrose on the thermodynamics of the aqueous cycloaddition of diene **6a** and buten-2-one [3]. Confirming the striking rate enhancements for some chemical transformations and in particular the Diels–Alder reaction [4,5], we showed that adding these carbohydrates provided another way of enhancing the hydrophobic effect.

An alternative way of influencing the system is to modify the carbohydrate moiety of the dienyl glycoside. Accordingly, we studied whether changing the nature of the glycosidic part of some glyco-organic dienes influenced the thermodynamics of their aqueous cycloaddition, and this is the purpose of the present report, where we describe the preparation of a variety of $\alpha$- and $\beta$-dienyl glycosides (mono- and di-saccharides) as well as the kinetic and thermodynamic data referring to their aqueous cycloaddition with buten-2-one.

## 2. Results and discussion

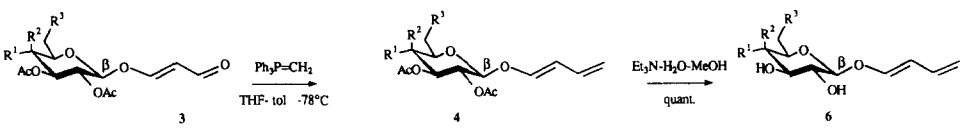
*Preparation of the dienes.*—Straightforward preparation of the 3-oxo-1-propenyl- and 1,3-butadienyl glycosides designed for preparing 1,3-butadienyl D-glucopyranosides




1 2 3

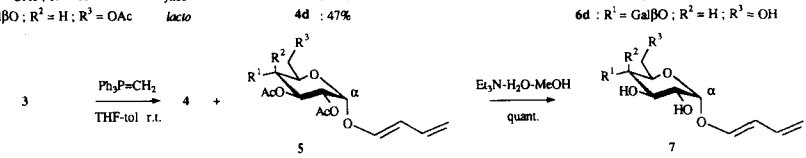
1a : $R^1$, $R^3$ = OAc; $R^2$ = H *gluco* 3a : ref 1
1b : $R^1$ = H ; $R^2$, $R^3$ = OAc *galacto* 3b : 66%
1c : $R^2$ = OAc ; $R^1$, $R^3$ = H *fuco* 3c : 77%
1d : $R^1$ = $Ac_4$GalβO ; $R^2$ = H ; $R^3$ = OAc *lacto* 3d : 65%

Scheme 1.




3 4 6

3a : $R^1$, $R^3$ = OAc; $R^2$ = H *gluco* 4a : ref 1 6a : $R^1$, $R^3$ = OH; $R^2$ = H
3b : $R^1$ = H ; $R^2$, $R^3$ = OAc *galacto* 4b : 77% 6b : $R^1$ = H ; $R^2$, $R^3$ = OH
3c : $R^1$ = H ; $R^2$ = OAc ; $R^3$ = H *fuco* 4c : 44% 6c : $R^1$ = H; $R^2$ = OH ; $R^3$ = H
3d : $R^1$ = $Ac_4$GalβO ; $R^2$ = H ; $R^3$ = OAc *lacto* 4d : 47% 6d : $R^1$ = GalβO ; $R^2$ = H ; $R^3$ = OH




3 4 + 5 7

α:β

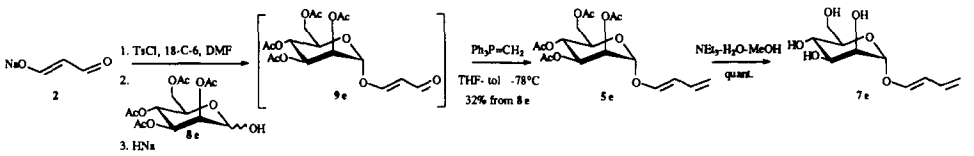
4a+5a : $R^1$, $R^3$ = OAc; $R^2$ = H : ref 1 75:25 7a : $R^1$, $R^3$ = OH; $R^2$ = H
4b+5b : $R^1$ = H ; $R^2$, $R^3$ = OAc : 50% 70:30 7b : $R^1$ = H ; $R^2$, $R^3$ = OH
4c+5c : $R^1$ = H ; $R^2$ = OAc ; $R^3$ = H : 75% 45:55 7c : $R^1$ = H; $R^2$ = OH ; $R^3$ = H

Scheme 2.

**6a** and **7a** [1,2] consisted first in the reaction of a protected pyranosyl bromide in dimethyl sulfoxide at room temperature with the sodium salt of malonaldehyde [6]. This afforded the aldehydes **3b–d** derived from galactose, fucose, and lactose in 66, 77 and 65% yields, respectively. This condensation was readily performed on multigram quantities, leading exclusively to β anomers (Scheme 1).

The Wittig methylenation of aldehydes **3b–d** with "salt-free" methylenetriphenylphosphorane in THF gave rise to the β-dienyl glycosides **4b–d** when the reaction was conducted at −78°C. Scheme 2 shows that the same reaction yielded mixtures of α and β anomers (**5b–c** and **4b–c**) when conducted at room temperature. This anomerization occuring at the aldehyde level under Wittig conditions has been consistently observed with this class of compounds [1–3]. Yields are given in Scheme 2. Quantitative deacetylation performed at room temperature in a 8:1:1 methanol–triethylamine–water mixture led quantitatively to the water-soluble dienes **6b–d** and **7b–c**.

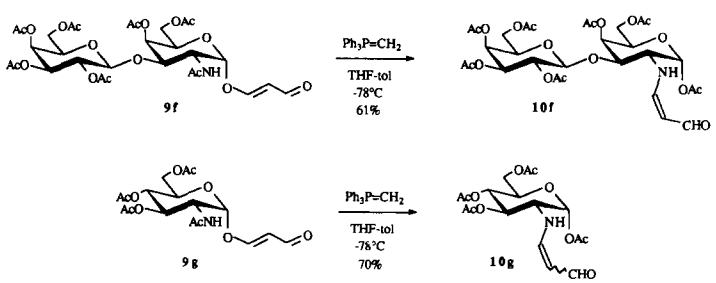
An alternative route was required for the manno derivative as its instability precluded



Scheme 3.

use of the conditions of the foregoing method. Thus, addition in DMF of the alcoholate produced from the reaction of sodium hydride with the anomeric alcohol **8e** [7] (obtained from penta-*O*-acetyl-D-mannopyranose by selective deacetylation of the anomeric acetate with hydrazine acetate [8]), on the 3-tosyloxy acrolein (prepared in situ from *p*-toluenesulfonyl chloride and the sodium salt of malonaldehyde) provided the unstable $\alpha$ aldehyde **9e** (Scheme 3), which was directly submitted to Wittig alkenation with methylene triphenylphosphorane in THF, giving rise to the buta-1,3-dienyl $\alpha$-D-mannopyranoside (**5e**) in 32% yield from **8e**. Further deacetylation ($MeOH–Et_3N–H_2O$) yielded quantitatively the water-soluble diene **7e**.

This methodology based on anomeric *O*-alkylation [9] was found especially efficient in the case of 2-acetamido-2-deoxy sugars, permitting, by use of an appropriate Wittig reagent, the introduction of a spacer with a natural 1,2-*cis* glycosidic linkage suitable for coupling to proteins [10]. Notably, we prepared aldehyde **9f** having the *T*-antigen disaccharide Gal-$\beta$-(1 → 3)-GalNAc as the glycosidic residue. The unusual presence of this residue at the surface of some tumoral cells motivated the preparation of some of its derivatives [11]. The interest here was in knowing whether this structure, also found in some proteins contained in the serum of an antarctic fish, could be responsible, potentially through special interactions with the water structure lattice, for their antifreeze effect. The corresponding butadienyl glycoside was thus the next target. However, in the methylenation step, it was observed that the 2-NHAc group interfered with the normal pathway of the reaction, and the reaction provided a product for which $^1H$ NMR patterns ($\delta$ 6.20 for 1-OAc equatorial hydrogen atom, $\delta$ 6.72 $J = 10$; 7; 3 Hz for a *Z* vinylic hydrogen atom) were consistent with structure **10f**. This product could



Scheme 4.

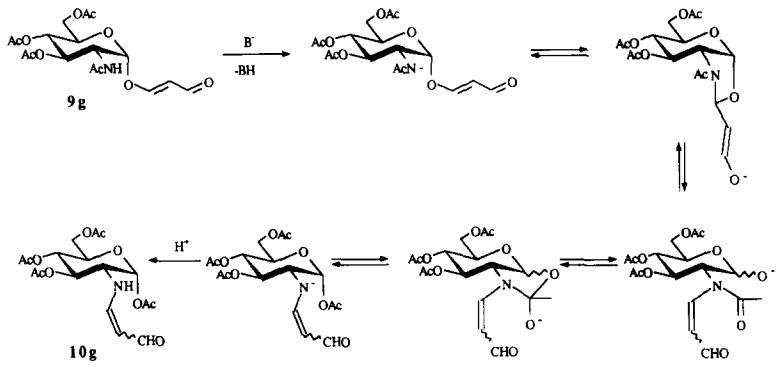
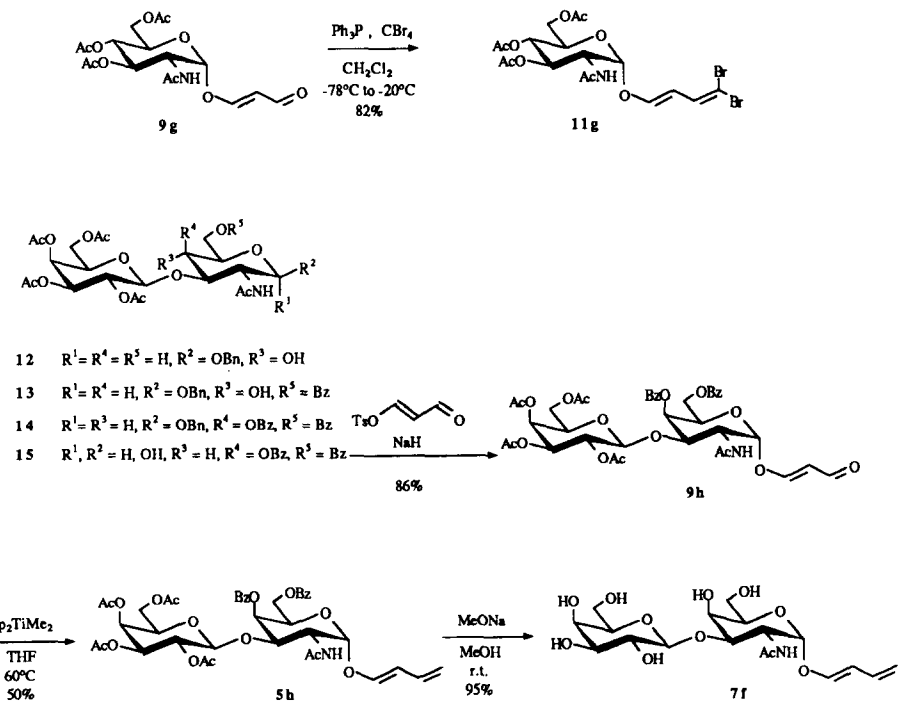


Fig. 2.



Scheme 5.

arise from exchange between the oxopropenyl and acetyl groups on the oxygen atom at C-1 and the nitrogen atom at C-2. This rearrangement was further proved in the case of aldehyde **9g** [10] derived from 2-acetamido-2-deoxy-D-glucose, which gave under the same conditions compound **10g** in 70% yield as a *E,Z* mixture (Scheme 4). A

Table 1
Second-order rate constants for the aqueous cycloadditions of glyco-organic dienes with buten-2-one at 25°C and their activation parameters

| Entry | Diene | $10^4$ $k_2$ ($M^{-1}$ $s^{-1}$) at 25°C | $\Delta H^{\neq}$ (kJ $mol^{-1}$) | $\Delta S^{\neq}$ (J $mol^{-1}$ $T^{-1}$) |
|---|---|---|---|---|
| 1 | *β-Glc* **6a** | 2.85 | 40.0 ± 0.6 | -178.8 ± 2.1 |
| 2 | *α-Glc* **7a** | 2.18 | 33.9 ± 1.0 | -180.7 ± 3.3 |
| 3 | *β-Gal* **6b** | 2.80 | 34.9 ± 0.8 | -195.6 ± 2.6 |
| 4 | *α-Gal* **7b** | 2.26 | 43.5 ± 0.1 | -168.1 ± 0.5 |
| 5 | *β-Fuc* **6c** | 2.70 | 38.9 ± 1.3 | -182.1 ± 4.3 |
| 6 | *α-Man* **7e** | 3.84 | 38.8 ± 2.1 | -179.7 ± 6.8 |
| 7 | *α-T* **7f** | 4.62 | 39.7 ± 1.0 | -175.1 ± 3.2 |
| 8 | *β-Lac* **6d** | 1.94 | 43.9 ± 2 .5 | -168.0 ± 2.5 |

mechanism of double migration involving an addition–elimination chain process is proposed for this reaction, as depicted in Fig. 1.

To support this hypothesis, we studied whether the basic character of the Wittig reagent was the cause of this double migration and found this to be the case. For example (Scheme 5), reaction of aldehyde **9g** with (the much less basic) dibromomethylene triphenylphosphorane [12] (obtained in situ from triphenylphosphine and carbon tetrabromide) gave the desired diene **11g** in 82% yield, whereas reaction of **9g** with sodium hydride led to the rearranged aldehyde **10g**, albeit in low yield. Furthermore, the chloromethylene phosphorane analog, having an intermediate basicity, led to a mixture of *Z* and *E* monochorinated dienes along with the transposed product. However, the presence of two terminal bromine atoms as in **11g** would imply a delicate reduction step on the way to the desired disaccharidic diene **7f**. This latter compound was obtained via an alternative route using a carbene-type reagent. Thus, reaction of aldehyde **9h** (obtained by the foregoing method from compound **15**, itself prepared from compound **12** [13] via inversion at C-4) with a modified [14] Tebbe reagent [15], {bis(cyclopentadienyldimethyltitanium), obtained by action of methyllithium on titanocene dichloride in ether [16]} produced diene **5h** in 50% yield. The moderate yield obtained in this methylenation step should be balanced with the fact that such carbenes are known to react also with ester carbonyl functions [17] frequently present in the substrates used. Finally, Zemplén deacetylation provided the desired diene **7f**. Although it was not possible to obtain a satisfactory elemental analysis for this diene, its structure was fully proved after total elucidation of its NMR spectra and its purity was further confirmed by analytical HPLC.

The sequence described completed the preparation of a range of eight water-soluble dienes designed to test the effect of the carbohydrate moiety on the thermodynamics of their aqueous cycloaddition with buten-2-one.

*Thermodynamic study.*—Having in hand a variety of butadienyl glycosides, the kinetics of their cycloaddition in water was first studied. Table 1 reports the second-order rate constants for the aqueous Diels–Alder reaction of dienes **6a–d** ($\beta$) and **7a,b,e,f** ($\alpha$) with buten-2-one, together with the activation enthalpies and entropies. The

Table 2
Second-order rate constants for the cycloadditions of dienes **6a**, **6b** and **7b** with buten-2-one in water or a water–methanol mixture at 25°C and their activation parameters

| Diene | Solvent | $10^4$ $k_2$ ($M^{-1}$ $s^{-1}$) | $\Delta H^{\neq}$ (kJ $mol^{-1}$) | $\Delta S^{\neq}$ (J $mol^{-1}$ $T^{-1}$) | $\Delta(\Delta H^{\neq})$ [b,c] (kJ $mol^{-1}$) | $-T\Delta(\Delta S^{\neq})$ [b,c] (kJ $mol^{-1}$) |
|---|---|---|---|---|---|---|
| β-*Glc* **6a** | $H_2O$ | 2.85 | 40.0 ± 0.6 | -178.8 ± 2.1 | -6.4 | +9.6 |
| β-*Glc* **6a** | MeOH-$H_2O$ [a] | 0.85 | 33.6 ± 0.8 | -211.1 ± 2.6 | | |
| β-*Gal* **6b** | $H_2O$ | 2.80 | 34.9 ± 0.8 | -195.6 ± 2.6 | -0.2 | +3.2 |
| β-*Gal* **6b** | MeOH-$H_2O$ [a] | 0.84 | 34.7 ± 2.0 | -206.3 ± 6.5 | | |
| α-*Gal* **7b** | $H_2O$ | 2.26 | 43.5 ± 0.1 | -168.1 ± 0.5 | -8.3 | +11.7 |
| α-*Gal* **7b** | MeOH-$H_2O$ [a] | 0.57 | 35.2 ± 0.2 | -207.5 ± 0.6 | | |

[a] 1:1 (v/v).
[b] from water to methanol–water.
[c] at 25°C.

importance of the hydroxyl group at C-6 on the behavior of β-D-galactosides is confirmed by comparing diene **6b** ( β-D-*galacto*) and **6c** ( β-D-*fuco*) (entries 3 and 5) on both the entropic and enthalpic factors. These two competitive effects compensate each other, thus making the rate constants nearly similar. The fastest of all dienes studied in reaction with buten-2-one in water is diene **7f** (entry 7) having as the carbohydrate residue the *T*-antigen disaccharide Gal-β-(1 → 3)-GalNAc, because of a decrease of activation entropy. However, the β-lactoside **6d** (entry 8) exhibits an even better fit with the water structure, as measured by the lowest activation entropy (in absolute value) in comparison with the other dienes, although a large enthalpic compensation effect leads in this case to the lowest rate. The effect of the antifreeze protein is probably more related to its tertiary structure.

We also studied whether changing the carbohydrate moiety would alter the sensitivity of the diene to a modification of the solvent. Thus measured were the rate constants and activation parameters for the reaction in 1:1 water–methanol for dienes **6a**, **6b** and **7b** ( β-D-*gluco*, β-D-*galacto* and α-D-*galacto*), products that were selected to provide insight into the influence of the anomeric configuration and that of a more distant axial hydroxyl group. Table 2 shows that the origin of the acceleration in pure water as compared to the water–methanol mixture is mostly due to the entropic term. This, along with our earlier findings, confirms Breslow's early proposal [5] concerning the role of hydrophobic effects as the essential cause of the rate enhancement. However, the high degree of cooperativity between the various hydroxyl groups in carbohydrates precludes interpretation of the subtle variations observed only in terms of axial or equatorial configurations. Nevertheless, important variations were observed for galactosyl dienes: indeed, reaction in water with diene **6b** ( β-D-*galacto*) is shown to have little sensitivity to solvent change in terms of activation entropy. As a matter of fact, reaction in water with this diene has the highest activation entropy in terms of absolute value (Table 1, entry 3), whereas diene **7b** ( α-D-*galacto*) behaves in an exactly opposite manner, giving for its reaction with buten-2-one the lowest activation entropy in absolute value (Table 1, entry 4) and the largest variation due to solvent change. This consistency between the

activation entropy of the reaction in water and the sensitivity of the reaction to solvent change, may be related to the hydration of such glyco-organic dienes relying on the fit of the carbohydrate moiety into the water structure, as proposed in Fig. 1, namely, the more the carbohydrate moiety fits into the water structure (low activation entropy) the more the reaction is sensitive to the solvent change. The striking behavior of galactose in water has already been observed in other studies [18,19].

## 3. Conclusion

A wide range of dienyl glycosides have been prepared. In the case of 2-acetamido-2-deoxy sugars, the pathway of the alkenation step using various Wittig reagents has been fully rationalized, and a concurrent migration reaction was circumvented by using carbene-type titanium derivatives.

In terms of thermodynamics, variations of activation parameters, albeit limited, were found upon changing the carbohydrate moiety in the dienyl glycosides. A direct relationship between activation entropy of the reaction in water and the sensitivity of the reaction to the solvent change was observed, notably in the $\alpha$-D- and $\beta$-D-*galacto* residues. This relationship may be interpreted by considering the fit of the carbohydrate moiety into the three-dimensional hydrogen-bond network of water, as proposed in our model for the hydration of such dienes.

## 4. Experimental

*General.*—Reactions were conducted under anhydrous $N_2$ atmosphere at room temperature except when otherwise specified. Solvents were freshly distilled before use. Buten-2-one, MeOH and water were distilled twice before use. Reactions were monitored using Merck $60F_{254}$ TLC plates. Flash chromatography was performed using 6-35$\mu$ silica gel purchased from S.D.S. Company. NMR spectra were recorded at 200 and 250 MHz with a Brüker AM 200 or 250 spectrometer (at 62 or 50 MHz for $^{13}C$). Chemical shifts are given in ppm downfield tetramethylsilane as internal reference. Coupling constants ($J$) are given in hertz, and the multiplicity is indicated with s for singlet, d for doublet, t for triplet, q for quadruplet, m for multiplet, and br for broad. Benzylic protons that give AB systems are described as fully resolved signals in order to facilitate comparison of the spectra. For chemical shift listing, atom numbering for aglycons (oxopropenyl and butadienyl residues) is consistent throughout the report using 1', 2', etc, with increasing numbers for farer atoms, even in disaccharides for which sugar name suffix is used for the secondary residue. Melting points were measured using a Reichert apparatus and are uncorrected. Molecular rotations were measured at 20°C with a Roussel-Jouan digital micropolarimeter. Known procedures were followed for preparing compounds **2** [6], **3a**, **4a**, **5a**, **6a**, **7a** [1], **8e** [7], **9f**, **9g** [10], and **12** [13].

*Kinetics.*—Pseudo-first-order rate constants were determined by monitoring the

disappearance of the diene (at 259 nm) with a computer controlled LKB Ultrospec II UV–visible spectrophotometer equipped with a Peltier effect temperature control of the cell holder. The rate constants were obtained from the perfectly linear portion of the curves from the initial stage of the reaction up to ca. 25% of transformation to avoid troubles due to very little deviations from the pseudo-first-order. In these conditions, all pseudo first order rate constants are reproducible to within 4% and each is obtained with a correlation coefficient better than 0.999. Isobaric activation parameters were obtained by using the Eyring equation with a least-square program at six temperatures between 20 and 40°C. This temperature range is compatible with the volatility of buten-2-one and MeOH and is commonly accepted for this type of experiments. Each experiment was run at least 3 times at a given set of conditions. Errors in $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were estimated from the standard deviation of the regression coefficient. The initial concentration were 0.5 mM for the diene and in the 130–150 mM range for buten-2-one. In each case, it was verified that no side reaction occurred in any significant extent by following the optical density of each partner alone.

*General procedure for the condensation of glycopyranosyl bromides with the sodium salt of malonaldehyde. Preparation of* (E)*-3-oxo-1-propenyl 2,3,4,6-tetra*-O*-acetyl-β-*D*-galactopyranoside* ***3b*** *and the* fuco *and* lacto *analogs* ***3c*** *and* ***3d***.—2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl bromide (**1b**) (5.43 g, 13.2 mmol) and the sodium salt of malonaldehyde [6] (2.50g, 26.4 mmol) were dissolved in anhyd $Me_2SO$ (30 mL) and allowed to stand at room temperature for 4 h. TLC ($Et_2O$) indicated total disappearance of the starting bromide. The mixture was then diluted with $Et_2O$ (300 mL) and washed with water (3 × 100 mL). The organic layer was dried over $MgSO_4$, concd under reduced pressure, and the residue was chromatographied ($Et_2O$) to give aldehyde **3b** (3.53 g, 66%). Compounds **3c** and **3d** were obtained following the same procedure, respectively, in 77 and 65% yield.

*(E)-3-Oxo-1-propenyl 2,3,4,6-tetra*-O*-acetyl-β-*D*-galactopyranoside* ***(3b).—[α]***$_D^{20}$ +10° (*c* 1.1, $CH_2Cl_2$); mp 113-114°C ($CH_2Cl_2$–$Et_2O$); $^1$H NMR (250 MHz, $CDCl_3$): δ 2.00–2.02 (4 s, 12 H, 4 Ac), 4.08 (m, 1 H, H-5), 4.18 (m, 2 H, H-$6_a$,$6_b$), 4.98 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 5.09 (dd, 1 H, $J_{2,3}$ 10.5, $J_{3,4}$ 3.5 Hz, H-3), 5.41 (dd, 1 H, H-2), 5.45 (d, 1 H, H-4), 5.81 (dd, 1 H, $J_{1',2'}$ 12.5, $J_{2',3'}$ 8 Hz, H-2'), 7.35 (d, 1 H, H-1'), 9.44 (d, 1 H, H-3'). Anal. Calcd for $C_{17}H_{22}O_{11}$ : C, 50.75; H, 5.51; O, 43.74. Found C, 50.52; H, 5.85; O, 43.72.

*(E)-3-Oxo-1-propenyl 2,3,4-tri*-O*-acetyl-β-*D*-fucopyranoside* ***(3c).—[α]***$_D^{20}$ +11° (*c* 1.0, $CH_2Cl_2$); $^1$H NMR (250 MHz, $CDCl_3$) δ 1.29 (d, 3 H, $J_{5\text{-Me}}$ 6 Hz, Me), 2.00–2.20 (3 s, 9 H, 3 Ac), 3.96 (q, 1 H, H-5), 4.94 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 5.08 (dd, 1 H, $J_{3,4}$ 3.5, $J_{2,3}$ 10 Hz, H-3), 5.30 (d, 1 H, H-4), 5.38 (dd, 1 H, H-2), 5.81 (dd, 1 H, $J_{1',2'}$ 13, $J_{2',3'}$ 8 Hz, H-2'), 7.35 (d, 1 H, H-1'), 9.43 (d, 1 H, H-3'). Anal. Calcd for $C_{15}H_{20}O_9$ : C, 52.32; H, 5.86; O, 41.82. Found: C, 52.41; H, 5.95; O, 41.76.

*(E)-3-Oxo-1-propenyl 2,2',3,3',4',6,6'-hepta*-O*-acetyl-β-*D*-lactopyranoside* ***(3d).—[α]***$_D^{20}$ −11° (*c* 1.3, $CH_2Cl_2$); mp 85–87°C ($CH_2Cl_2$–$Et_2O$); $^1$H NMR (250 MHz, $CDCl_3$): δ 1.98–2.16 (5 s, 21 H, 7 Ac), 4.52 (d, 1 H, $J_{1,2}$ 8 Hz, H-1 Gal), 4.97 (dd, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 3 Hz, H-3 Gal), 5.01 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 5.12 (m, 2 H, 2 H-2), 5.26 (t, 1 H $J_{2,3} = J_{3,4}$ 8 Hz, H-3), 5.36 (d, 1 H, H-4 Gal), 5.70 (dd, 1 H, $J_{1',2'}$ 12, $J_{2',3'}$

8 Hz, H-2'), 7.30 (d, 1 H, H-1'), 9.43 (d, 1 H, H-3'). Anal. Calcd for $C_{29}H_{38}O_{19}$ : C, 50.43; H, 5.55; O, 44.02. Found: C, 50.30; H, 5.73; O, 43.91.

*General procedure for the Wittig reactions using "salt-free" triphenyl methylene phosphorane. Preparation of (E)-buta-1,3-dienyl 2,3,4,6-tetra-O-acetyl-α- and β-D-galactopyranosides* ***4b*** *and* ***5b*** *and the peracetylated dienes* fuco *and* lacto ***4c-d*** *and* ***5c.*** —To a soln of the aldehyde **3b** (0.90g, 0.24 mmol) in anhyd THF (10 mL) was added dropwise triphenylmethylenephosphorane (0.78M in toluene, 3 mL). A stock solution of this reagent was prepared by action of sodium amide in liquid ammonia on methyltriphenylphosphonium bromide followed by evaporation of ammonia, dissolution in anhyd toluene and filtration over Celite. The Wittig reaction was followed by TLC using pure $Et_2O$ as eluent. After 15 min at room temperature, $Et_2O$ was added (30 mL) and the organic layer was washed with water (2 × 10 mL), dried over sodium sulfate and concd under reduced pressure. Flash-chromatography of the residue (1:1:3 $CH_2Cl_2$–$Et_2O$–hexane) provided first the less polar α diene **5b** (0.311 g, 35%) followed by the β diene **4b** (0.136 g, 15%). When the same reaction was conducted at -78°C, only the β diene **4b** was obtained in a 77% yield. Using this same procedure starting from aldehydes **3c** and **3d**, the following yields were obtained; from aldehyde **3c** at -78°C, diene **4c** was produced in a 44% yield, and at room temperature, a 45:55 mixture of **5c** and **4c** in a 75% combined yield; from aldehyde **3d** at −78°C, diene **4d** was obtained in 47% yield.

*(E)-Buta-1,3-dienyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside* ***(4b)***.—$[\alpha]_D^{20}$ +13.5° (*c* 0.9, $CH_2Cl_2$); mp 79.5–80°C ($CH_2Cl_2$–$Et_2O$); $^1H$ NMR (250 MHz, $CDCl_3$) δ 2.01, 2.08, 2.18 (3 s, 3, 6 and 3 H, 4 Ac), 4.00 (m, 1 H, H-5), 4.17 (m, 2 H, H-$6_a$,$6_b$), 4.76 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.95 (d, 1 H, $J_{3',4'(E)}$ 10.5 Hz, H-4'(*E*)), 5.05 (dd, 1 H, $J_{2,3}$ 10.5, $J_{3,4}$ 3.5 Hz, H-3), 5.08 (d, 1 H, $J_{3',4'(Z)}$ 17 Hz, H-4'(*Z*)), 5,33 (dd, 1 H, H-2), 5.42 (d, 1 H, H-4), 5.84 (dd, 1 H, $J_{1',2'}$ 11.5, $J_{2',3'}$ 10.5 Hz, H-2'), 6.20 (dt, 1 H, $H_{3'}$), 6.53 (d, 1 H, H-1'). Anal. Calcd for $C_{18}H_{24}O_{10}$ : C, 53.99; H, 6.04; O, 39.96. Found: C, 54.00; H, 5.99; O, 38.91.

*(E)-Buta-1,3-dienyl 2,3,4-tri-O-acetyl-β-D-fucopyranoside* ***(4c)***.—$[\alpha]_D^{20}$ +16° (*c* 0.9, $CH_2Cl_2$); $^1H$ NMR (250 MHz, $CDCl_3$): δ 1.25 (d, 3 H, $J_{5\text{-Me}}$ 6 Hz, Me), 2.00, 2.07, 2.20 (3 s, 9 H, 3 Ac), 3.88 (q, 1 H, H-5), 4.72 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.93 (d, 1 H, $J_{3',4'(E)}$ 10.5 Hz, H-4'(*E*)), 5.05 (dd,1 H, $J_{2,3}$ 10, $J_{3,4}$ 3.5 Hz, H-3), 5.07 (d, 1 H, $J_{3',4'(Z)}$ 17 Hz, H-4'(*Z*)), 5,26 (d, 1 H, H-4), 5.30 (dd, 1 H, H-2), 5.83 (dd, 1 H, $J_{1',2'}$ 11.5, $J_{2',3'}$ 10.5 Hz, H-2'), 6.20 (dt, 1 H, H-3'), 6.53 (d, 1 H, H-1'). Anal. Calcd for $C_{16}H_{22}O_8$ : C, 56.13; H, 6.48; O, 37.39. Found: C, 56.11; H, 6.56; O, 37.25.

*(E)-Buta-1,3-dienyl 2,2',3,3',4',6,6'-hepta-O-acetyl-β-D-lactopyranoside* ***(4d)***.—$[\alpha]_D^{20}$ −5° (*c* 1.0, $CH_2Cl_2$); $^1H$ NMR (250 MHz, $CDCl_3$): δ 1.97–2.15 (21 H, 7 Ac), 4.49 (d, 1 H, $J_{1,2}$ 8 Hz, H-1 Gal), 4.77 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.95 (m, 3 H, H-2, H-3 Gal, H-4'(*E*)), 5.08 (d, 1 H, $J_{3',4'(Z)}$ 17 Hz, H-4'(*Z*)), 5.12 (dd,1 H, $J_{2,3}$ 10 Hz, H-2 Gal), 5.23 (t, 1 H, $J_{2,3} = J_{3,4}$ 9 Hz, H-3), 5.36 (d, 1 H, $J_{3,4}$ 3.5 Hz, H-4 Gal), 5.80 (dd, 1 H, $J_{1',2'}$ 11.5, $J_{2',3'}$ 10.5 Hz, H-2'), 6.15 (dt, 1 H, H-3'), 6.50 (d, 1 H, H-1'). Anal. Calcd for $C_{30}H_{40}O_{18}$ : C, 52.32; H, 5.85; O, 41.82. Found: C, 52.20; H, 5.80; O, 41.85.

*(E)-Buta-1,3-dienyl 2,3,4,6-tetra-O-acetyl-α-D-galactopyranoside* ***(5b)***.—$[\alpha]_D^{20}$ +172° (*c* 1, $CH_2Cl_2$); mp 113–114°C ($CH_2Cl_2$–$Et_2O$); $^1H$ NMR (250 MHz, $CDCl_3$): δ 2.02, 2.03, 2.09, 2.15 (4 s, 12 H, 4 Ac), 4.00–4.25 (m, 3 H, H-5, H-$6_a$,$6_b$), 4.95 (d, 1

H, $J_{3',4'(E)}$ 10.5 Hz, H-4'(*E*)), 5.10 (d, 1 H, $J_{3',4'(Z)}$ 17 Hz, H-4'(*Z*)), 5.19 (dd, 1 H, $J_{1,2}$ 3.5, $J_{2,3}$ 10.5 Hz, H-2), 5.42 (m, 2 H, H-1, H-3), 5.49 (d, 1 H, $J_{3,4}$ 3.5 Hz, H-4), 5.90 (dd, 1 H, $J_{1',2'}$ 11.5, $J_{2',3'}$ 10.5 Hz, H-2'), 6.20 (dt, 1 H, H-3'), 6.50 (d, 1 H, H-1'). Anal. Calcd for $C_{18}H_{24}O_{10}$ : C, 53.99; H, 6.04; O, 39.96. Found: C, 53.95; H, 6.06; O, 39.92.

*(*E*)-Buta-1,3-dienyl 2,3,4-tri-*O*-acetyl-α-*D*-fucopyranoside (**5c**).*—$[\alpha]_D^{20}$ +193° (*c* 0.9, $CH_2Cl_2$); $^1$H NMR (250 MHz, $CDCl_3$): δ 1.15 (d, 3 H, $J_{5\text{-Me}}$ 6 Hz, Me), 2.01, 2.08, 2.19 (3s, 9 H, 3 Ac), 4.15 (q, 1 H, H-5), 4.99 (d, 1 H, $J_{3',4'(E)}$ 10.5 Hz, H-4'(*E*)), 5.09 (d, 1 H, $J_{3',4'(Z)}$ 17 Hz, H-4'(*Z*)), 5.18 (dd, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 3.5 Hz, H-3), 5.33 (m, 2 H, H-1,4), 5.42 (dd, 1 H, $J_{1,2}$ 3, $J_{2,3}$ 10 Hz, H-2), 5.88 (dd, 1 H, $J_{1',2'}$ 11.5, $J_{2',3'}$ 10.5 Hz, H-2'), 6.21 (dt, 1 H, H-3'), 6.51 (d, 1 H, H-1'). Anal. Calcd for $C_{16}H_{22}O_8$ : C, 56.13; H, 6.48; O, 37.39. Found: C, 56.28; H, 6.40; O, 37.32.

*General procedure for deacetylation of protected dienes. Preparation of (*E*)-buta-1,3-dienyl β-*D*-galactopyranoside (**6b**) and dienes **6c-d** and **7b,c**.*—The acetylated diene **4b** (1.45 g, 3.68 mmol) was treated for 12 h at room temperature in a 8:1:1 MeOH–$Et_3N$–water mixture. Evaporation to dryness followed by several coevaporations with water gave the diene **6b** (0.84 g, 100%) that could be lyophilized. The same quantitative yield of diene **6c**, **6d**, **7b**, and **7c** were obtained following the same process starting, respectively, from **4c**, **4d**, **5b** and **5c**.

*(*E*)-Buta-1,3-dienyl β-*D*-galactopyranoside (**6b**).*—$[\alpha]_D^{20}$ +28° (*c* 3.15, water); mp 154–157°C (lyophilized powder); $^1$H NMR (250 MHz, $CD_3OD$): δ 3.49 (dd, 1 H, $J_{2,3}$10, $J_{3,4}$ 3.5 Hz, H-3), 3.60 (m, 1 H, H-5), 3.63 (dd, 1 H, $J_{1,2}$ 8 Hz, H-2), 3.74 (m, 2 H, H-$6_a$,$6_b$), 3.85 (d, 1 H, H-4), 4.52 (d, 1 H, H-1), 4.82 (d, 1 H, $J_{3',4'(E)}$ 10.5 Hz, H-4'(*E*)), 4.98 (d, 1 H, $J_{3',4'(Z)}$ 17 Hz, H-4'(*Z*)), 5.79 (dd, 1 H, $J_{1',2'}$ 12, $J_{2',3'}$ 10.5 Hz, H-2'), 6.23 (dt, 1 H, H-3'), 6.72 (d, 1 H, H-1'). Anal. Calcd for $C_{10}H_{16}O_6$ : C, 51.72; H, 6.95; O, 41.34. Found: C, 52.01; H, 6.94; O, 41.23.

*(*E*)-Buta-1,3-dienyl β-*D*-fucopyranoside (**6c**).*—$[\alpha]_D^{20}$ −7° (*c* 0.9, water); mp 144–146°C (lyophilized powder); $^1$H NMR (200 MHz, $CD_3OD$): δ 1.28 (d, 3 H, $J_{5\text{-Me}}$ 6 Hz, Me), 3.48 (dd, 1 H, $J_{2,3}$10, $J_{3,4}$ 3.5 Hz, H-3), 3.58 (dd, 1 H, $J_{1,2}$ 8 Hz, H-2), 3.62 (m, 1 H, H-4), 3.72 (q, 1 H, H-5), 4.48 (d, 1 H, H-1), 4.82 (d, 1 H, $J_{3',4'(E)}$ 10.5 Hz, H-4'(*E*)), 4.98 (d, 1 H, $J_{3',4'(Z)}$ 17 Hz, H-4'(*Z*)), 5.77 (t, 1 H, $J_{1',2'} = J_{2',3'}$ 10.5 Hz, H-2'), 6.23 (dt, 1 H, H-3'), 6.67 (d, 1 H, H-1'). Anal. Calcd for $C_{10}H_{16}O_5$ : C, 55.55; H, 7.46; O, 37.00. Found: C, 55.59; H, 7.34; O, 36.72.

*(*E*)-Buta-1,3-dienyl β-*D*-lactopyranoside (**6d**).*—$^1$H NMR (250 MHz, $CD_3OD$): δ 4.47(d, 1 H, $J_{1,2}$ 8 Hz, H-1 Gal), 4.60 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.84 (d, 1 H, $J_{3',4'(E)}$ 10.5 Hz, H-4'(*E*)), 5.00 (d, 1 H, $J_{3',4'(Z)}$ 17 Hz, H-4'(*Z*)), 5.79 (t, 1 H, $J_{1',2'} = J_{2',3'}$ 10.5 Hz, H-2'), 6.25 (dt, 1 H, H-3'), 6.72 (d, 1 H, H-1'). Anal. Calcd for $C_{16}H_{26}O_{11} + H_2O$ : C, 46.60; H, 6.84; O, 46.56. Found: C, 47.14; H, 6.99; O, 45.78.

*(*E*)-Buta-1,3-dienyl α-*D*-galactopyranoside (**7b**).*—$[\alpha]_D^{20}$ +134° (*c* 1.05, water); $^1$H NMR (250 MHz, $CD_3OD$): δ 3.68 (m, 2 H, H-$6_a$,$6_b$), 3.80 (m, 3 H, H-2,3,5), 3.92 (d, 1 H, $J_{3,4}$ 3.5 Hz, H-4), 4.83 (d, 1 H, $J_{3',4'(E)}$ 10.5 Hz, H-4'(*E*)), 5.00 (d, 1 H, $J_{3',4'(Z)}$ 17 Hz, H-4'(*Z*)), 5.13 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.86 (dd, 1 H, $J_{1',2'}$ 12, $J_{2',3'}$ 10 Hz, H-2'), 6.25 (dt, 1 H, H-3'), 6.67 (d, 1 H, H-1'). Anal. Calcd for $C_{10}H_{16}O_6$ : C, 51.72; H, 6.95; O, 41.34. Found: C, 51.38; H, 7.20; O, 41.45.

*(E)-Buta-1,3-dienyl α-D-fucopyranoside (7c).*—$[\alpha]_D^{20}$ +130° (*c* 1, water); mp 131–133°C (lyophilized powder); $^1$H NMR (250 MHz, $CD_3OD$): δ 1.20 (d, 3 H, $J_{5\text{-Me}}$ 6 Hz, Me), 3.68 (m, 1 H, H-4), 3.79 (m, 2 H, H-2,3), 3.92 (q, 1 H, $H_5$), 4.83 (d, 1 H, $J_{3',4'(E)}$ 10.5 Hz, H-4'(*E*)), 4.99 (d, 1 H, $J_{3',4'(Z)}$ 17 Hz, H-4'(*Z*)), 5.07 (d, 1 H, $J_{1,2}$ 3 Hz, H-1), 5.33 (t, 1 H, $J_{1',2'} = J_{2',3'}$ 10.5 Hz, H-2'), 6.25 (dt, 1 H, H-3'), 6.63 (d, 1 H, H-1'). Anal. Calcd for $C_{10}H_{16}O_5$ : C, 55.55; H, 7.46; O, 37.00. Found: C, 55.35; H, 7.37; O, 37.10.

*(E)-Buta-1,3-dienyl 2,3,4,6-tetra-O-acetyl-α-D-mannopyranoside (5e).*—A solution of the sodium salt of malonaldehyde [6] (2.5 g, 25.8 mmol), *p*-toluenesulfonyl chloride (3.30 g, 17.2 mmol) and 18-C-6 crown ether (140 mg, cat.) in freshly distilled anhyd THF (60 mL) was stirred at room temperature until TLC (1:1 $Et_2O$–pentane) showed complete consumption of chloride (UV). After ~ 15 min, a solution of 2,3,4,6-tetra-*O*-acetyl-D-mannopyranose (**8e**) [7] (3.0 g, 5.61 mmol) in THF (15 mL) was added and the mixture was cooled to −20° C. Sodium hydride (60% wt. in mineral oil, 0.5 g, 12.5 mmol) was added and the reaction was monitored by following the appearance of the aldehyde (TLC, $Et_2O$). After 30 min at −20°C, the mixture was diluted with $Et_2O$ (200 mL) and was washed with phosphate pH 7 buffer (2 × 100 mL). The organic layer was dried over $MgSO_4$ and the filtrate was immediately filtered through a 5 cm plug of silica gel (70–200 mesh) and eluted with $Et_2O$. After evaporation of the solvent under reduced pressure and drying under high vacuum, the obtained foam was dissolved in anhydrous THF (40 mL) and treated with triphenylmethylene phosphorane (0.6 M solution in toluene, 15 mL, 9 mmol). After 30 min, the mixture was diluted with $Et_2O$ (200 mL) and washed with phosphate pH 7 buffer (2 × 100 mL) and brine (2 × 50 mL). After evaporation of the solvent, flash-chromatography of the residue (1:1:3 $Et_2O$–$CH_2Cl_2$–pentane) produced diene **5e** (1.10 g, 32%); $[\alpha]_D^{20}$ +53° (*c* 1.1, $CH_2Cl_2$); $^1$H NMR (250 MHz, $CDCl_3$) δ 2.02, 2.06, 2.09, 2.18 (4s, 12 H, 4 Ac), 3.97 (ddd, 1 H, $J_{4,5}$ 9.5, $J_{5,6a}$ 2, $J_{5,6b}$ 5 Hz, H-5), 4.12 (dd, 1 H, $J_{6a,6b}$ 12 Hz, H-$6_a$), 4.28 (dd, 1 H, H-$6_b$), 4.96 (d, 1 H, $J_{3',4'(E)}$ 10.5 Hz, H-4'(*E*)), 5.11 (d, 1 H, $J_{3',4'(Z)}$ 17 Hz, H-4'(*Z*)), 5.30–5.42 (m, 4 H, H-1,2,3,4), 5.91 (dd, 1 H, $J_{1',2'}$ 12, $J_{2',3'}$ 10.5 Hz, H-2'), 6.20 (dt, 1 H, H-3'), 6.49 (d, 1 H, H-1'). Anal. Calcd for $C_{18}H_{24}O_{10}$ : C, 53.99; H, 6.04; O, 39.96. Found: C, 53.99; H, 6.12; O, 39.83.

*(E)-Buta-1,3-dienyl α-D-mannopyranoside (7e).*—Following the general procedure for deacetylation of dienes, **7e** was obtained quantitatively from **5e**; $[\alpha]_D^{20}$ +39° (*c* 1.25, water); $^1$H NMR (250 MHz, $CD_3OD$) δ 3.48 (m, 1 H, H-5), 3.70 (m, 3 H, H-4,$6_a$,$6_b$), 3.80 (dd, 1 H, $J_{2,3}$ 2.5, $J_{3,4}$ 12 Hz, H-3), 3.87 (dd, 1 H, $J_{1,2}$ 2 Hz, H-2), 4.84 (d, 1 H, $J_{3',4'(E)}$ 10.5 Hz, H-4'(*E*)), 5.00 (d, 1 H, $J_{3',4'(Z)}$ 17 Hz, H-4'(*Z*)), 5.07 (d, 1 H, H-1), 5.80 (t, 1 H, $J_{1',2'} = J_{2',3'}$ 10.5 Hz, H-2'), 6.24 (dt, 1 H, H-3'), 6.67 (d, 1 H, H-1'). Anal. Calcd for $C_{10}H_{16}O_6$ : C, 51.72; H, 6.95; O, 41.34. Found: C, 51.50; H, 7.13; O, 41.42.

*1,3,4,6-Tetra-O-acetyl-2-deoxy-2-[(3-oxo-(E,Z)-1-propenyl)-amino]-α-D-glucopyranose (10g).*—When treating aldehyde **9g** [10] following the general procedure for Wittig methylenation using salt-free triphenylmethylene phosphorane at -78°C, transposed aldehyde **10g** was obtained as a mixture of *E* and *Z* isomers in a 70% yield. Preparing in situ the Wittig reagent from methyltriphenyl phosphonium bromide and butyllithium led to similar yields. (Starting from aldehyde **9f** [10], compound **10f** was

obtained in a 61% yield.) $^1$H NMR data for 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-1,4,6-tri-*O*-acetyl-2-deoxy-2-[(*Z*)-3-oxo-1-propenyl)-amino]-α-δ-galactopyranose (**10f**): (250 MHz, $CDCl_3$): δ 1.95–2.25 (7s, 21 H, 7 Ac), 3.68 (dt, 1 H, $J_{1,2}$ 3.5, $J_{2,3} = J_{2,NH}$ 10 Hz, H-2), 3.80–4.23 (m, 7 H, 2 H-5, H-3, 4 H-6), 4.58 (d, 1 H, $J_{1,2}$ 8 Hz, H-1 Gal), 4.94 (dd, 1 H, $J_{3,4}$ 3 Hz, H-3), 5.08 (m, 1 H, H-2'), 5.14 (dd, 1 H, $J_{2,3}$ 10Hz, H-2 Gal), 5.36 (d, 1 H, H-4), 5.50 (d, 1 H, $J_{3,4}$ 3 Hz, H-4 Gal), 6.20 (d, 1 H, H-1), 6.72 (ddd, 1 H, $J_{1',NH}$ 10, $J_{1',2'}$ 7, $J_{1',3'}$ 3 Hz, H-1'), 9.17 (m, 1 H, H-3'), 9.94 (br t, 1 H, NH); $^{13}$C NMR (50 MHz, $CDCl_3$): δ 20.68, 29.75, 91.31, 96.41, 101.32, 153.07, 189.25. Data for **10g**: partial separation of *E* and *Z* isomers allowed to assign the following patterns: $^1$H NMR (250 MHz, $CDCl_3$, isomer *E*): δ 3.70–3.80 (m, 1 H, H-2), 5.20 (t, 1 H, $J_{3,4} = J_{4,5}$ 10 Hz, H-4), 5.37 (t, 1 H, $J_{2,3}$ 10 Hz, H-3), 5.43 (dd, 1 H, $J_{1',2'}$ 10, $J_{2',3'}$ 8 Hz, H-2'), 6.25 (d, 1 H, $J_{1,2}$ 4 Hz, H-1), 7.00 (m, 1 H, H-1'), 9.13 (d, 1 H, H-3'). $^1$H NMR (250 MHz, $CDCl_3$, isomer *Z*) δ 3.52 (dt, 1 H, $J_{1,2}$ 4, $J_{2,3} = J_{2,NH}$ 10 Hz, H-2), 5.08 (dd, 1 H, $J_{1',2'}$ 7.5, $J_{2',3'}$ 2 Hz, H-2'), 5.12 (t, 1 H, $J_{3,4} = J_{4,5}$ 10 Hz, H-4), 5.36 (t, 1 H, H-3), 6.22 (d, 1 H, H-1), 6.68 (ddd, 1 H, $J_{1',NH}$ 12, $J_{1',3'}$ 3 Hz, H-1'), 9.17 (dd, 1 H, H-3'), 9.74 (br dd, 1 H, NH). Anal. Calcd for $C_{17}H_{23}NO_{16}$: C, 50.87; H, 5.78; O, 39.86; N 3.49. Found: C, 50.89; H, 5.70; O, 39.75; N, 3.70.

*(E)-4,4-Dibromo-buta-1,3-dienyl 3,4,6-tri-O-acetyl-2-acetamido-2-deoxy-α-D-glucopyranoside (**11g**).*—To a solution of aldehyde **9g** [10] (0.150 g, 0.37 mmol) and triphenylphosphine (0,485 g, 1.85 mmol) in $CH_2Cl_2$ (3 mL) cooled to −60°C was added a solution of $CBr_4$ (0.245 g, 0.74 mmol) in $CH_2Cl_2$ (1 mL). When warming until −20°C, the colorless solution progressively turned to an orange colored solution. At −20°C, all the starting aldehyde was converted to a less polar product (TLC 1:1 toluene–acetone). This mixture was directly applied on a silica gel column and eluted (6:1 toluene–acetone) to yield the dibromodiene **11g** (0.170 g, 82%); $^1$H NMR (250 MHz, $CDCl_3$) δ 1.98, 2.06, 2.11 (3 s, 3, 6 and 3 H, 3 Ac), 3.93 (ddd, 1 H, $J_{4,5}$ 9, $J_{5,6a}$ 3.5, $J_{5,6b}$ 2 Hz, H-5), 4.09 (dd, 1 H, $J_{6a,6b}$ 12 Hz, H-$6_b$), 4.24 (dd, 1 H, H-$6_a$), 4.42 (dt, 1 H, $J_{1,2} = 3$, $J_{2,3} = J_{2,NH}$ 9 Hz, H-2), 5.15–5.32 (m, 3 H, H-1,3,4), 5.87 (d, 1 H, NH), 5.96 (dd, 1 H, $J_{1',2'}$ 12, $J_{2',3'}$ 10.5 Hz, H-2'), 6.68 (d, 1 H, H-3'), 6.80 (d, 1 H, H-1'). Anal. Calcd for $C_{18}H_{23}NO_9Br_2$ : C, 38.80; H, 4.16; N, 2.51; Br, 28.68. Found: C, 38.26; H, 4.31; N, 2.11; Br, 25.66.

*Benzyl 3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-acetamido-6-O-benzoyl-2-deoxy-β-D-glucopyranoside (**13**).*—To a soln of diol **12** [13] (5.133 g, 7.99 mmol) in pyridine (32 mL) maintained at 0°C was added dropwise benzoyl chloride (0.93 mL, 8 mmol). When TLC (EtOAc) indicated total disappearance of the starting diol (2 h), MeOH (1 mL) was added, and the mixture was allowed to warm to room temperature and was then diluted with $CH_2Cl_2$. The organic layer was washed with 2 N HCl (2 × 50 mL) and brine (50 mL) and was dried over $MgSO_4$. After evaporation of the solvent, flash-chromatography of the residue (1:3 hexane–EtOAc) allowed to isolate alcohol **13** (5.75 g, 96%) as a white solid that could be crystallized from $CH_2Cl_2$–$Et_2O$–hexane. $[\alpha]_D^{20}$ −10° (*c* 1.1, EtOAc); mp 115°C ($CH_2Cl_2$–$Et_2O$); $^1$H NMR (250 MHz, $Me_2SO$-$d_6$): δ 1.84, 1.91, 1.98, 2.03, 2.12 (5s, 15 H, 5 Ac), 3.43 (m, 1 H, H-2), 3.53-3.75 (m, 3 H, H-3,4,5), 4.01 (dd, 1 H, $J_{5,6}$ 6, $J_{6,6'}$ 11 Hz, H-6 Gal), 4.11(dd, 1 H, $J_{5,6'}$ 6, $J_{6,6'}$ 11 Hz, H-6' Gal), 4.22 (t, 1 H, H-5 Gal), 4.42 (dd, 1 H, $J_{5,6}$ 5, $J_{6,6'}$ 12 Hz,

H-6), 4.47 (d, 1 H, $J_{1,2}$ 9 Hz, H-1), 4.52 (d, 1 H, $J$ 12 Hz, $CH_2Ph$), 4.60 (d, 1 H, H-6), 4.73 (d, 1 H, $J$ 12 Hz, $CH_2Ph$), 4.82 (d, 1 H, $J_{1,2}$ 8 Hz, H-1 Gal), 4.96 (dd, 1 H, $J_{2,3}$ 10 Hz, H-2 Gal), 5.14 (dd, 1 H, $J_{3,4}$ 3.5 Hz, H-3 Gal), 5.27 (d, 1 H, H-4 Gal), 7.20–7.35 (m, 5 H, Bn), 7.53–7.73 (m, 3 H, Bz), 7.98–8.04 (d, 1 H, $J_{NH,2}$ 8 Hz, NH), 8.02 (m, 2 H, Bz); $^{13}C$ NMR (50 MHz, $Me_2SO$-$d_6$): δ 20.42, 22.97, 53.94, 60.98, 63.77, 67.16, 68.34, 69.51, 69.91, 70.42, 73.31, 82.26, 100.07, 127.32, 128.16, 128.85, 129.19, 129.62, 133.43, 137.67, 148.58, 165.59, 169.08, 169.31, 169.49, 169.90. Anal. Calcd for $C_{36}H_{43}NO_{16}$: C, 57.98; H, 5.81; O, 34.33; N, 1.87. Found: C, 57.72; H, 6.04; O, 34.06; N, 1.95.

*Benzyl 3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-acetamido-4,6-di-O-benzoyl-2-deoxy-β-D-galactopyranoside (**14**).*—To a soln of alcohol **13** (0.825 g, 1.106 mmol) in pyridine (5.5 mL) maintained at 0°C was added trifluoromethanesulfonyl anhydride (0.27 mL, 1.66 mmol). When TLC (4:1 $CH_2Cl_2$–acetone) indicated total disappearance of the starting alcohol (3 h), the mixture was diluted with $CH_2Cl_2$. The organic layer was washed with ice-cooled 2 N HCl (2 × 20 mL) and ice-cooled brine (20 mL). After evaporation of the solvent until a 10 mL volume was reached, the solution was filtered on a short pad of silica gel eluted with EtOAc. The solvent was then evaporated and the residue was dissolved in toluene (20 mL). Tetrabutylammonium benzoate (2.0 g, 5.5 mmol) and 4 Å molecular sieves (2 g) were added, and the mixture was warmed at 50°C. After 1 h, $Et_2O$ (100 mL) was added, and the organic phase was washed with water (5 × 50 mL) in order to remove the excess of ammonium salts. The organic layer was then dried over $MgSO_4$, filtered and the solvent was evaporated. Flash-chromatography of the residue (7:1 $CH_2Cl_2$–acetone) allowed to isolate compound **14** (0.74 g, 79%) that could be crystallized from a $CH_2Cl_2$–$Et_2O$. $[\alpha]_D^{20}$ +10° (*c* 1.0, EtOAc); mp 103–105°C ($CH_2Cl_2$–$Et_2O$–hexane); $^1H$ NMR (250 MHz, $CDCl_3$): δ 1.88–2.04 (m, 15 H, 5 Ac), 3.57 (m, 1 H, H-2), 3.80–4.18 (m, 4 H, 2 H-5 and 2 H-6 Gal), 4.40–4.53 (m, 2 H, 2 H-6), 4.59 (d, 1 H, $J$ 12 Hz, $CH_2Ph$), 4.68 (d, 1 H, $J_{1,2}$ 8 Hz, H-1), 4.84 (dd, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 3 Hz, H-3), 4.89 (d, 1 H, $J$ 12 Hz, $CH_2Ph$), 4.93 (dd, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 3 Hz, H-3 Gal), 5.07 (dd, 1 H, $J_{1,2}$ 8 Hz, H-2 Gal), 5.18 (d, 1 H, H-1 Gal), 5.27 (d, 1 H, H-4 Gal), 5.75 (d, 1 H, H-4), 5.82 (d, 1 H, $J_{NH,2}$ 8 Hz, NH), 7.30–7.35 (m, 5 H, Bn), 7.40–7.60 (m, 6 H, Bz), 8.07 (m, 4 H, Bz); $^{13}C$ NMR (50 MHz, $CDCl_3$): δ 20.42, 55.55, 60.86, 63.28, 66.75, 69.27, 70.73, 70.91, 71.15, 71.80, 75.11, 98.78, 100.33, 128.19, 129.51, 129.85, 130.16, 132.93, 137.03, 165.77, 166.08, 169.07, 169.86, 170.01, 170.61. Anal. Calcd for $C_{43}H_{47}NO_{17}$: C, 60.77; H, 5.58; O, 32.01; N, 1.65. Found: C, 60.46; H, 5.64; O, 32.24; N, 1.72.

*(E)-3-Oxo-1-propenyl 3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-acetamido-4,6-di-O-benzoyl-2-deoxy-α-D-galactopyranoside (**9h**).*—A solution of benzyl glycoside **14** (1.47 g, 1.73 mmol) in EtOAc (34 mL) was stirred under $H_2$ (5 atm) in the presence of 10% Pd/C (0.9 g) for 24 h (TLC 1:1 toluene–acetone). Filtration on celite followed by evaporation of the solvent provided quantitatively 3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-acetamido-4,6-di-*O*-benzoyl-2-deoxy-D-galactopyranose (**15**) (anomeric mixture, 1.32 g) as a white solid. $^1H$ NMR for **15α**: (250 MHz, $CDCl_3$): δ 1.95-2.10 (m, 15 H, 5 Ac), 4.27 (dd, 1 H, $J_{2,3}$ 11, $J_{3,4}$ 3 Hz, H-3), 4.73 (d, 1 H, $J_{1,2}$ 8 Hz, H-1 Gal), 4.97 (dd, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 3 Hz, H-3 Gal), 5.14 (dd, 1 H, H-2

Gal), 5.33 (d, 1 H, H-4 Gal), 5.52 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.74 (d, 1 H, $J_{3,4}$ 3 Hz, H-4), 6.07 (d, 1 H, $J_{NH,2}$ 8 Hz, NH), 7.30–7.60 (m, 6 H, Bz), 7.95–8.10 (m, 4 H, Bz); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 20.58, 23.16, 42.92, 61.00, 63.07, 66.64, 67.28, 68.42, 69.76, 70.83, 72.48, 91.86, 100.06, 128.26, 128.36, 129.69, 129.95, 133.10, 165.78, 166.29, 169.65, 170.12, 170.25, 170.41, 170.81. A solution of sodium salt of malonaldehyde [6] (0.1 g, 1.06 mmol), toluenesulfonyl chloride (0.076 g, 0.4 mmol) and 18-C-6 crown ether (20 mg, cat.) in freshly distilled anhyd THF (10 mL) was strirred at room temperature until TLC (1:1 $Et_2O$–pentane) showed complete consumption of chloride (UV). After ~ 30 min, the mixture was cooled to −78°C and a solution of **15** (0.165 g, 0.26 mmol) in THF (5 mL) was added. Sodium hydride (60% wt. in mineral oil, 1.2 mmol) was added and the reaction was monitored by following the appearance of the aldehyde (TLC, 1:1.2 toluene–acetone). After 30 min at −20°C, the mixture was diluted with $CH_2Cl_2$ (100 mL) and was poured into ice-cooled phosphate pH 7 buffer. The organic layer was washed with brine (2 × 20 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash-chromatography of the residue (2:1 toluene–acetone) allowed to isolate compound **9h** ($\alpha/\beta$ = 9:1, 0.185 g, 86%) as a white foam. $[\alpha]_D^{20}$ +58° (*c* 1.2, EtOAc); $^1$H NMR (250 MHz, $CDCl_3$), α anomer, δ 1.90–2.11 (m, 15 H, 5 Ac), 4.24 (dd, 1 H, $J_{2,3}$ 11, $J_{3,4}$ 3 Hz, H-3), 4.77 (d, 1 H, $J_{1,2}$ 8 Hz, H-1 Gal), 4.98 (dd, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 3.5 Hz, H-3 Gal), 5.22 (dd, 1 H, H-2 Gal), 5.36 (d, 1 H, H-4 Gal), 5.78 (d, 1 H, $J_{3,4}$ 3 Hz, H-4), 5.83 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.85 (dd, 1 H, $J_{1',2'}$ 12, $J_{2',3'}$ 8 Hz, H-2'), 6.11 (d, 1 H, $J_{NH,2}$ 7 Hz, NH), 7.29 (d, 1 H, H-1'), 9.25 (d, 1 H, H-3'); $^{13}$C NMR (50 MHz, $CDCl_3$); δ 20.44, 20.62, 23.01, 38.60, 48.99, 61.00, 62.78, 66.55, 68.16, 68.75, 69.34, 70.75, 71.05, 71.87, 99.23, 99.94, 114.19, 128.40, 129.54, 129.97, 133.31, 166.55, 166.91, 166.45, 169.72, 170.02, 170.29, 170.63, 190.89. Anal. Calcd for $C_{39}H_{43}NO_{18}$ : C, 57.56; H, 5.33; N, 1.72. Found: C, 57.85; H, 5.45; N, 1.80.

*(E)-Buta-1,3-dienyl 3-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-2-acetamido-4,6-di-O-benzoyl-2-deoxy-α-D-galactopyranoside (**5h**).*—The aldehyde **9h** (0.320 g, 0.393 mmol) was treated with 4 mL of a 0.5 M soln of $Cp_2TiMe_2$ in THF (prepared as described in ref 14) at 60°C away from light (due to the instability to light of the titanium complex). After 3.5 h, the mixture was cooled to room temperature, diluted with $Et_2O$ (10 mL) and filtered on a 5 cm plug of silica gel. Elution with $Et_2O$ allowed to remove most of titanium complex byproducts while organic compounds were recuperated after further elution with EtOAc. This latter layer was concd and flash-chromatography of the residue (1:2 hexane–EtOAc) produced diene **5h** (0.160 g, 50%); $[\alpha]_D^{20}$ +59° (*c* 1.4, EtOAc); mp 114–115°C (EtOH); $^1$H NMR (200 MHz, $CDCl_3$) δ 1.96–2.09 (15 H, 5 Ac), 3.87–3.97 (m, 2 H, 2 H-5), 4.01–4.16 and 4.30–4.46 (2m, 4 H, 4 H-6), 4.20 (dd, 1 H, $J_{2,3}$ 11, $J_{3,4}$ 3 Hz, H-3), 4.66–4.79 (m, 1 H, H-2), 4.73 (d, 1 H, $J_{1,2}$ 8 Hz, H-1 Gal), 4.89 (d, 1 H, $J_{3',4'(E)}$ 10 Hz, H-4'(*E*)), 4.96 (dd, 1 H, $J_{2,3}$ 10, $J_{3,4}$ 3 Hz, H-3 Gal), 5.02 (d, 1 H, $J_{3',4'(Z)}$ 16 Hz, $H_{4'(Z)}$), 5.17 (dd, 1 H, H-2 Gal), 5.33 (d, 1 H, H-4 Gal), 5.45 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-1), 5.74 (d, 1 H, H-4), 5.79–5.97 (m, 2 H, H-2', NH), 6.10 (dt, 1 H, $J_{2',3'}$ 10 Hz, H-3'), 6.52 (d, 1 H, $J_{1',2'}$ 12 Hz, H-1'), 7.35–7.65 (m, 6 H, Ar), 7.90–8.10 (m, 4 H, Ar); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 20.68, 23.31, 48.95, 97.33, 100.10, 112.85, 114.41, 133.02, 133.32, 146.19, 170.06. Anal. Calcd for

$C_{40}H_{45}NO_{17}$: C, 59.18; H, 5.59; O, 33.51; N, 1.73. Found: C, 58.84; H, 6.02; O, 33.29; N, 1.80.

*(E)-Buta-1,3-dienyl 3-O-(β-D-galactopyranosyl)-2-acetamido-2-deoxy-α-D-galactopyranoside (7f).*—To a soln of diene **5h** (65 mg, 0.08 mmol) in anhyd MeOH (5 mL) was added a soln of NaOMe in MeOH (1 M, 0.2 mL). After 3 h at room temperature, the mixture was neutralized with acidic resin (Amberlite IR-120), filtered and concd under reduced pressure, giving **7f** as a white solid (33 mg, 95%) which proved to be pure by analytical HPLC (inverse phase $C_{18}$, length 250mm, diameter 4.6mm, 1 mL/min of 75:25 water–MeOH, retention time 17.64 min); $[\alpha]_D^{20}$ +153° (*c* 0.6, water); $^1$H NMR (250 MHz, $D_2O$): δ 3.87 (d, 1 H, $J_{3,4}$ 3 Hz, H-4 Gal), 4.07 (dd, 1 H, $J_{2,3}$ 11, $J_{3,4}$ 3 Hz, H-3), 4.24 (d, 1 H, H-4), 4.38 (d, 1 H, $J_{1,2}$ 3.5 Hz, H-2), 4.45 (d, 1 H, $J_{1,2}$ 8 Hz, H-1 Gal), 4.92 (d, 1 H, $J_{3',4'(E)}$ 10 Hz, H-4'(*E*)), 5.09 (d, 1 H, $J_{3',4'(Z)}$ 17 Hz, H-4'(*Z*)), 5.19 (d, 1 H, H-1), 5.90 (t, 1 H, $J_{1',2'} = J_{2',3'}$ 10 Hz, H-2'), 6.29 (dt, 1 H, H-3'), 6.63 (d, 1 H, H-1'); $^{13}$C NMR (50 MHz, $D_2O$) δ 21.82, 47.94, 60.88, 68.47, 70.43, 71.26, 72.35, 74.89, 76.75, 97.18, 104.67, 112.14, 113.81, 132.74, 146.91.

## Acknowledgements

This work was supported by the Centre National de la Recherche Scientifique and the Université de Paris-Sud. We gratefully acknowledge the Rhône-Poulenc Company for a grant to H.B.

## References

[1] A. Lubineau and Y. Queneau, *Tetrahedron Lett.*, 26 (1985) 2653-2654; A. Lubineau and Y. Queneau, *J. Org. Chem.*, 52 (1989) 1001–1007.
[2] A. Lubineau and Y. Queneau, *Tetrahedron*, 45 (1989) 6697–6712.
[3] A. Lubineau, H. Bienaymé, Y. Queneau, and M.-C. Scherrmann, *New J. Chem.*, 18 (1994) 279–285.
[4] A. Lubineau, J. Augé, and Y. Queneau, *Synthesis*, (1994) 741–760; C.-J. Li, *Chem. Rev.*, 93 (1993) 2023-2035; W.A. Herrmann and C.W. Kohlpaintner, *Angew. Chem., Int. Ed. Engl.*, 32 (1993) 1524–1544; W. Blokzijl and J.B.F.N. Engberts, *Angew. Chem., Int. Ed. Engl.*, 32 (1993) 1545–1579.
[5] U. Pindur, G. Lutz, and C. Otto, *Chem. Rev.*, 93 (1993) 741–761; D.C. Rideout and R. Breslow, *J. Am. Chem. Soc.*, 102 (1980) 7816–7817; R. Breslow, *Acc. Chem. Res.*, 24 (1991) 159–164.
[6] T.V. Protopopova and A.P. Skoldinov, *Zh. Obshch. Khim.*, 28 (1958) 240–243; *Chem. Abs.*, 52 (1958) 12754c.
[7] J. Kerekgyarto, J.P. Kamerling, J.B. Bouwstra, J.F.G. Vliegenthart, and A. Liptak, *Carbohydr. Res.*, 186 (1989) 51–62; K. Watanabe, K. Itoh, Y. Araki, and Y. Ishido, *Carbohydr. Res.*, 154 (1986) 165–176; J.G. Douglas and J. Honeyman, *J. Chem. Soc.*, (1955) 3674–3681; A.M. Gakhokidze and N.D. Kutidze, *Zh. Obshch. Khim.*, 22 (1952) 247–251.
[8] G. Excoffier, D. Gagnaire, and J.-P. Utille, *Carbohydr. Res.*, 39 (1975) 368–373.
[9] R.R. Schmidt, *Angew. Chem., Int. Ed. Engl.*, 25 (1986) 212–235.
[10] A. Lubineau, H. Bienaymé, and J. Le Gallic, *J. Chem. Soc., Chem. Commun.*, (1989) 1918–1919.
[11] A. Lubineau and H. Bienaymé, *Carbohydr. Res.*, 212 (1991) 267–271.
[12] E.J. Corey and P.L. Fuchs, *Tetrahedron Lett.*, 36 (1972) 3769–3772.
[13] C. Augé and A. Veyrières, *Carbohydr. Res.*, 46 (1976) 293–298.

[14] N.A. Petasis and E.I. Bzowej, *J. Am. Chem. Soc.*, 112 (1990) 6392–6394.
[15] F.N. Tebbe, G.W. Parshall, and G.S. Reddy, *J. Am. Chem. Soc.*, 100 (1978) 3611–3613; L.F. Cannizzo and R.H. Grubbs, *J. Org. Chem.*, 50 (1985) 2386–2387.
[16] K. Clauss and H. Bestian, *Justus Liebigs Ann. Chem.*, 654 (1962) 8–19.
[17] S.H. Pine, R. Zahler, D.A. Evans, and R.H. Grubbs, *J. Am. Chem. Soc.*, 102 (1980) 3270–3272.
[18] S.A. Galema, M.J. Blandamer, and J.B.F.N. Engberts, *J. Am. Chem. Soc.*, 112 (1990) 9665–9666; S.A. Galema and H. Høiland, *J. Phys. Chem.*, 95 (1991) 5321–5326; S.A. Galema, M.J. Blandamer, and J.B.F.N. Engberts, *J. Org. Chem.*, 57 (1992) 1995–2001; S.A. Galema, J.B.F.N. Engberts, H. Høiland, and G.M. Førland, *J. Chem. Phys.*, 97 (1993) 6885–6889.
[19] M.D. Walkinshaw, *J. Chem. Soc., Perkin Trans. 2*, (1987) 1903–1906.