for 15 min, a solution of ketone **28** (80 mg, 0.17 mmol) in THF (2 mL) was introduced, and the mixture was stirred under nitrogen an additional 10 min. Ethyl iodide (137 μL, 1.70 mmol) was added and the resulting mixture stirred at −30 °C for 6 h, after which saturated aqueous ammonium chloride was added. The mixture was diluted with ethyl acetate, the organic layer separated, and the aqueous phase extracted with ethyl acetate. The crude reaction mixture was separated by flash chromatography (1:1–3:1 ethyl acetate–hexane), affording 70 mg of compound **30a** (87%) and 5 mg of starting material.

(±)-1-(Phenylsulfonyl)-5-nor-15-oxocoronaridine (33). A stirred solution of **7a** (50 mg, 0.11 mmol) and sodium hexamethyldisilazide (240 μL of α 1 M solution in THF, 0.24 mmol) in THF (2 mL) was stirred at 0 °C for 15 min. The mixture was cooled at −30 °C, and ethyl iodide (88 mL, 1.11 mmol) was added. Stirring was maintained for 14 h, at which time saturated aqueous ammonium chloride was introduced and the mixture allowed to warm to room temperature. The solution was partitioned between water and ethyl acetate. The separation of the reaction mixture by flash chromatography (1:4–1:1 ethyl acetate–hexane) afforded 6 mg (11%) of **33** and 22 mg (44%) of the starting material **7a**.

(±)-16-Carbomethoxy-20-deethyl-1-(phenylsulfonyl)-15-oxo-20,21-didehydrocleavamine (35a, 35b). A. Using Lithium Diisopropylamide. To a stirred solution of diisopropylamine (15 μL, 0.11 mmol) in THF (2 mL) at 0 °C was added 60 μL (0.10 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. After the resultant mixture was stirred for 15 min, a solution of ketone **20** (30 mg, 0.07 mmol) in THF (1 mL) was added and the mixture stirred under nitrogen for 10 min. Ethyl iodide (52 μL, 0.65 mmol) was added and the resulting mixture stirred at 0 °C for 6 h, after which saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate. Separation of the reaction mixture by flash chromatography (1:1–3:1 ethyl acetate–hexane) afforded 13 mg of starting material and 16 mg (53%) of compound **35a,35b** as a 3:1 mixture.

B. Using Sodium Hexamethyldisilylamide. A stirred solution of compound **20** (40 mg, 0.09 mmol) and NaHMDSA (0.18 mL of a 1 M solution in THF, 0.19 mmol) in THF (2 mL) was stirred at 0 °C for 15 min. The mixture was cooled at −78 °C, and ethyl iodide (69 μL, 0.86) was added. The temperature was raised to −10 °C, and stirring was maintained for 2 h. After addition of a saturated solution of ammonium chloride, the mixture was extracted with ethyl acetate. Separation by flash chromatography (3:1 ethyl acetate–hexane) afforded 19 mg (48%) of **35a,35b** as a 1:1 mixture.

Direct Comparison of Fragmentation of 7a, 20, and 28. A solution of each ketone in THF at −25 °C was treated with 1.3 equiv of LDA. Aliquots were removed at 2-h intervals, quenched in aqueous acetonitrile, and analyzed on a C-18 reversed-phase column using aqueous acetonitrile. The ratios of materials are shown:

time	7a:[34]	20:35	28:30
2	100:0	44:56	19:81
4	100:0	50:50	10:90
6	100:0	49:51	10:90
10	100:0	52:48	12:88
22	100:0	46:54	9:91

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Water-Catalyzed Amide Hydrolysis in Dilute Aqueous Carbohydrate Solutions

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Rates and thermodynamic activation parameters were determined for the water-catalyzed hydrolysis of the activated amide bond in three 1-acyl-1,2,4-triazoles of different hydrophobicity by using dilute aqueous solutions of simple carbohydrates as the reaction medium. The solutions show thermodynamically almost ideal behavior. It appears that the kinetic medium effects, and, in particular, the changes in $\Delta^{\ddagger}S^{\ominus}$, are largely determined by carbohydrate-induced alterations in the three-dimensional hydrogen-bond network of water. The specific hydration model for carbohydrates, developed by Franks and his associates, appears to provide a key to the understanding of the carbohydrate medium effects on the hydrolytic model reaction.

In recent years there has been much effort expended to understand the effect of aqueous reaction media on chemical reactivity.[1-3] The approach usually involves perturbation of the aqueous medium by the addition of (non)electrolytes and an analysis of the response of rates and thermodynamic activation parameters in terms of initial state and transition state solvation. However, the addition of small amounts of the additive has usually drastic consequences and leads to the introduction of new intermolecular interactions involving the additive as one component and the initial state and/or transition state as the other component. Furthermore, relatively hydrophobic additives tend to form clusters even in dilute solutions.[4,5] All these specific effects are extremely difficult to separate from effects arising from a perturbation of the motional, spatial, or orientational correlations in the hydrogen-bond network of water as induced by the additive. These difficulties pertain to both "typically aqueous" (TA) and "typically nonaqueous" (TNA) solutions.[6]

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(7) For highly dilute aqueous binary solutions, a quantitative treatment for kinetic solvent effects has recently been advanced: (a) Blokzijl, W.; Jager, J.; Engberts, J. B. F. N.; Blandamer, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6411. The background is given in: (b) Savage, J. J.; Wood, R. H. *J. Solut. Chem.* **1976**, *5*, 733.

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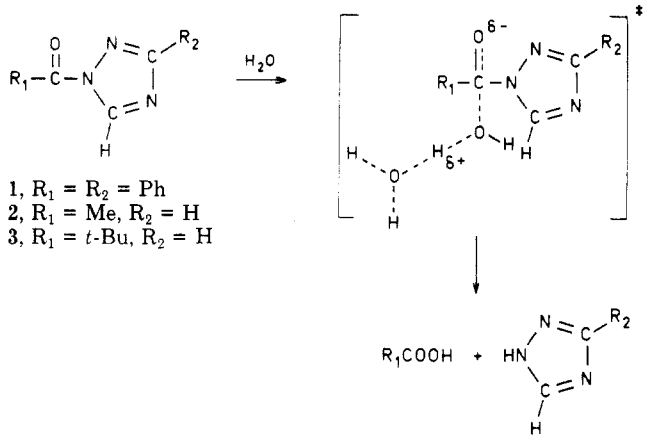
Scheme I



1, $R_1 = R_2 = Ph$
2, $R_1 = Me$, $R_2 = H$
3, $R_1 = t\text{-}Bu$, $R_2 = H$

Herein we present an attempt to gain more insight into kinetic water-structure effects. The unique solvent properties of liquid water are associated with the three-dimensional hydrogen-bond regime which allows constant fluctuations between forms of water with different geometry and density.[8] Despite Ben-Naim's elegant definition of water structure in terms of the average number of hydrogen bonds per water molecule,[9] the concept is difficult to quantify.[10] But trends in "structure making" or "structure breaking" abilities are experimentally accessible for a wide variation of solutes including a series of simple carbohydrates.[11] Thus we have measured rates and activation parameters for a water-catalyzed hydrolysis reaction in the presence of 0–4 mol % of simple carbohydrates which modify water structure in a different manner. These carbohydrate solutions are semi-ideal, their properties being mainly determined by hydration of the OH groups in the different anomers and conformers present in solution.[11] The hydrogen-bond interactions involved in these hydration processes are very similar in strength to those which govern water–water interactions. We find that the subtle but specific influences which simple carbohydrates exert on water structure and which seem to be determined largely by their stereochemistry are indeed revealed in the activation parameters of the hydrolytic model reaction. These results also possess biochemical relevance since carbohydrates are usually abundantly present at biological membrane surfaces[12] and particularly the carbohydrates of cell membrane glycoproteins may play a role in determining biochemical transformations near membrane interfaces.[13]

Results and Discussion

The hydrolytic reaction that we have chosen for study is the water-catalyzed (i.e., pH-independent) hydrolysis of the 1-acyl-1,2,4-triazoles **1–3** (Scheme I). This reaction proceeds in the pH region between 3 and 5 via a dipolar transition state containing two water molecules and in which three protons are in flight.[14] Previous studies have illustrated the medium dependence of the pseudo-first-order rate constants (k_{obsd})[7,15] and which, particularly in the presence of hydrophobic cosolvents, is accompanied by large, partly compensatory changes in $\Delta^{\ddagger}H^{\ominus}$ and $\Delta^{\ddagger}S^{\ominus}$.[16] The hydrolysis has also been studied in the presence of micelles[17] and water-soluble polymers containing hydrophobic microdomains.[18]

Pseudo-first-order rate constants and (isobaric) activation parameters for neutral hydrolysis of **1–3** in water and in aqueous solutions of a series of simple carbohydrates are listed in Table I. The rate constants pertain to hydrolysis since no carbohydrate-derived esters are found in

Table I. Pseudo-First-Order Rate Constants and Activation Parameters for the Neutral Hydrolysis of the 1-Acyl-1,2,4-triazoles 1–3 in Aqueous Solutions of Carbohydrates at 25 °C

compd	carbohydr	conc, mol %	$10^5 k_{obsd}$, s^{-1}	$\Delta^{\ddagger}H^{\ominus}$, kJ mol^{-1}	$\Delta^{\ddagger}S^{\ominus}$, J mol^{-1} K^{-1}
1[a]			124	48.7 ± 0.7	−137 ± 2
1[b]	D-glucose	4.0[c]	77	50.9 ± 0.3	−134 ± 1
1	D-xylose	4.0	67	50.6 ± 0.3	−135 ± 1
1	maltose	2.0	75	50.3 ± 0.7	−136 ± 2
1	D-ribose	4.0[d]	86	47.0 ± 0.7	−146 ± 3
1	D-arabinose	4.0	93	47.0 ± 0.3	−145 ± 2
2			219	42.4 ± 0.6	−154 ± 2
2	D-glucose	4.0[c]	174	42.9 ± 0.6	−154 ± 2
2	D-ribose	4.0[d]	157	40.8 ± 0.3	−162 ± 1
3			337	38.0 ± 0.3	−165 ± 1
3	D-glucose	4.0[c]	320	39.3 ± 0.9	−161 ± 3
3	D-ribose	4.0[d]	254	37.0 ± 0.8	−171 ± 3

[a] $\Delta^{\ddagger}V^{\ominus} = -15.8 \pm 0.7$ cm^3 mol^{-1}.[16] [b] $\Delta^{\ddagger}V^{\ominus} = -17.2 \pm 3$ cm^3 mol^{-1}. [c] $\epsilon = 70.3$. [d] $\epsilon = 73.3$.

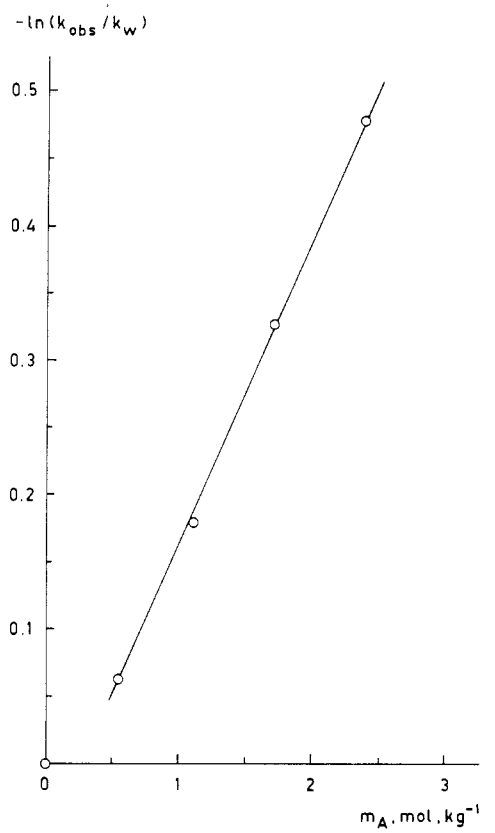


Figure 1. Plot of $-\ln (k_{obsd}/k_w)$ vs. molality of D-glucose for the neutral hydrolysis of **1** at 25 °C.

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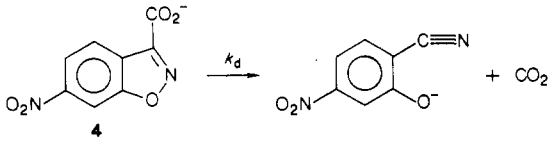
the reaction products. The observation that for 1 a plot of ln (k_{obsd}/k_w) vs. molality (m_A) of D-glucose (k_w is the rate constant in water) is linear (Figure 1) indicates that carbohydrate–carbohydrate interactions do not contribute to the kinetic medium effects in the employed concentration range. The straight line in Figure 1 does not exactly pass through the origin, but this effect does not originate from thermodynamic nonideal behavior since it is known that limiting apparent molar volumes are concentration independent between at least 0 and 2 mol % of D–glucose.[19]

All carbohydrates are found to retard the rates of hydrolysis of 1–3. In order to substantiate that the addition of the carbohydrates leads to only small changes in solvent polarity, we have also measured first-order rate constants (k_d, 30 °C) for the unimolecular decarboxylation of 6-nitrobenzisoxazole-3-carboxylate (4) in water (k_d = 7.40 × 10^{-6} s^{-1}) and in aqueous solutions containing 4 mol % of D-glucose (k_d = 8.23 × 10^{-6} s^{-1}) and 4 mol % of D-ribose (k_d = 8.75 × 10^{-6} s^{-1}). Like many other decarboxylations,[20]



4

the reaction of 4 is very sensitive to medium effects.[21] Therefore, the above rate constants clearly illustrate the small perturbation of solvent properties induced by the carbohydrates.

Perhaps the most striking feature emerging from consideration of the kinetic data for 1–3 in Table I is concerned with the $\Delta^{\ddagger}H^{\ominus}$–$\Delta^{\ddagger}S^{\ominus}$ compensation behavior. Taking pure water as the reference, it is found that $\Delta^{\ddagger}S^{\ominus}$ remains unchanged or increases slightly for D-glucose, D-xylose, and maltose (a dimer of D-glucose), whereas a decrease of $\Delta^{\ddagger}S^{\ominus}$ is observed for D-ribose and D-arabinose. Interestingly, a similar trend in behavior is found for the hydrolysis of 2 and 3 despite the considerable difference in hydrophobicity in the series 1-3 as expressed by the sum of Rekker's hydrophobic fragmental constants[22] for R_1 and R_2 (1, $\sum f_i$ = 3.77; 2, $\sum f_i$ = 0.88; 3, $\sum f_i$ = 2.55). Thus, $\Delta^{\ddagger}S^{\ominus}$ becomes more negative in the presence of D-ribose and D-arabinose, an effect not observed for the other three carbohydrates. It is tempting to seek an explanation for this difference in terms of the specific hydration model for simple carbohydrates as advanced by Franks and others.[11,19,23,24] In this model, the hydration behavior of simple carbohydrates is related with the possibility of maximum matching of spacings and mutual orientations of the OH vectors in the carbohydrate with those in unperturbed (i.e., "lattice") water. Largely based on consideration of notional hydration numbers and limiting apparent molal volumes of polyhydroxy compounds in water, it is argued that *equatorial* OH groups of carbohydrates fit better into water structure than *axial* OH groups. This explains the fact that transfer of a carbohydrate from a nonaqueous solvent to water is accompanied by an increase of the proportions of those conformers with the maximum number of equatorial OH groups.[24,25] In terms of this theory, one could expect that those carbohydrates which fit nicely into the water lattice (D-glucose, D-xylose, maltose) and which, therefore, exert only small effects on water structure, will have almost no effect on $\Delta^{\ddagger}S^{\ominus}$ for the hydrolysis reaction. The data in Table I show that this is borne out in practice. Consistent with this interpretation, the volumes of activation ($\Delta^{\ddagger}V^{\ominus}$) for hydrolysis of 1 in water and in 4 mol % D-glucose are also equal within experimental error. By contrast, those carbohydrates for which the majority of OH groups is less capable of hydrogen bonding to lattice water (i.e., D-ribose and D-arabinose)[26] induce rate retardations governed by a decrease in $\Delta^{\ddagger}S^{\ominus}$, apparently because in these less-structured aqueous media more entropy is lost in the formation of the heavily hydrated dipolar transition state.

Table II. Thermodynamic Parameters for Transfer of 5 from Water to Aqueous Carbohydrate Solutions at 25 °C

carbohydr	conc, mol %	$\Delta G_t^{\ominus}$, kJ mol^{-1}	$\Delta H_t^{\ominus}$, kJ mol^{-1}	$\Delta S_t^{\ominus}$, J mol^{-1} K^{-1}
D-glucose	4.0	−0.68 ± 0.2	1.6 ± 1.5	8 ± 5
D-ribose	4.0	−2.50 ± 0.1	−11.1 ± 2.1	−29 ± 7

As a further check for the interpretation of the kinetic results, thermodynamic parameters have been determined for the transfer of a model substrate (for 1), the nonhydrolyzable 1-phenacyl-3-phenyl-1,2,4-triazole (5), from water to 4 mol % solutions of D-glucose and D-ribose (Table II). Since this solute is hydrophobic and "structure-making", more entropy will be lost upon transfer from water to a less-structured aqueous medium. Indeed, $\Delta S_t^{\ominus}$ is strongly negative for transfer to the aqueous solution of D-ribose. Transfer to the D-glucose solution is accompanied by only very small values of $\Delta H_t^{\ominus}$ and $\Delta S_t^{\ominus}$ (Table II).

Finally, we return to the rate retardation induced by D-glucose (Table I, Figure 1). An endeavor can be made to analyse this rate inhibition in terms of the recently developed Savage–Wood treatment.[7] The basic equation is given in eq 1, in which C, S, and TS refer to carbohydrate, substrate, and transition state, respectively, m_A is the molality of the carbohydrate, m^0 = 1 mol kg^{-1}, $g_{C\text{-}S}$ and $g_{C\text{-}TS}$ are Gibbs function substrate–carbohydrate and transition state–carbohydrate pairwise interaction parameters,[27] n is the number of water molecules in the transition state, ϕ is the practical osmotic coefficient for the solution, and M_1 is the molar mass of water. We assume that the solvation change during the activation process is dominated by interactions involving three polarized OH groups in the transition state.[7a] Applying the "additivity principle"[7b] and taking ϕ = 1 for the concentration range employed,[28] we obtain[7a] eq 2. Herein the G parameters

$$\ln (k_{obsd}/k_w) = (2/RT)(1/m^0)^2 (g_{C\text{-}S} - g_{C\text{-}TS})m_A - n\phi m_A M_1 \quad (1)$$

$$\ln (k_{obsd}/k_w) = 3(2/RT) \times (1/m^0)^2(-5G_{OH\leftrightarrow OH} - 3.5G_{CH_2\leftrightarrow OH} - G_{O\leftrightarrow OH})m_A - 2m_A M_1 \quad (2)$$

refer to pairwise group interaction parameters.[7b] In D-glucose there are 5 OH groups, one O moiety, whereas the five C–H and one CH_2 groups are together equivalent to 3.5 CH_2 groups.[7b] If we take reasonable G values (i.e., $G_{OH\leftrightarrow OH}$ = −81 J kg mol^{-2}, $G_{CH_2\leftrightarrow OH}$ = +48 J kg mol^{-2}, and $G_{O\leftrightarrow OH}$ = −31 J kg mol^{-2}),[7] the slope of the linear plot of

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ln (k_{obsd}/k_w) vs. m_A is calculated as +0.62. This large and positive value deviates strongly from the experimental slope (-0.24). This deviation is significant, even when allowance is made for the approximations inherent in the Savage-Wood treatment. The most likely explanation again emphasizes the idea that the equatorial OH groups of D-glucose fit well into water structure and make them (almost) indistinguishable from those of bulk water. As a consequence, the term $-5G_{OH\leftrightarrow OH}$ in eq 2 is much too large. Good agreement between the experimental and calculated slope is obtained by taking 0.6 OH groups into account in eq 2, indicating that 4.4 OH groups fit into the water structure. This value is in satisfactory agreement with the experimental value of 3.7 equatorial OH moieties.[24] However, we note that much more work will be necessary to further substantiate the Savage-Wood approach (including the applicability of the "additivity principle") in the analysis of carbohydrate medium effects in aqueous solution.

In summary, we submit that the subtle influences which simple carbohydrates exert on water structure and which are largely determined by their stereochemistry are indeed revealed in the isobaric activation parameters of the pH-independent hydrolysis of 1-acyl-1,2,4-triazoles. Thermodynamic parameters for transfer of a model substrate from water to aqueous solutions of D-glucose and D-ribose as well as an analysis of the rate inhibition in the presence of D-glucose in terms of a Savage-Wood treatment support the interpretation.

Experimental Section

Materials. The carbohydrates were high quality commercial samples: D-glucose (Merck), D-xylose (Merck), maltose (Janssen), D-ribose (Janssen), and D-arabinose (Janssen). The 1-acyl-1,2,4-triazoles **1–3** were prepared by acylation of the corresponding 1,2,4-triazole. The model substrate **5** was prepared from the reaction of phenacyl bromide with 3-phenyl-1,2,4-triazole. The product was purified by chromatography over neutral alumina using ether–methanol (9:1) as the eluent. 6-Nitrobenzisoxazole-3-carboxylate (**4**) was synthesized according to the literature procedure.[30]

Products. ^{1}H NMR spectroscopic analysis revealed that carboxylic acid and (substituted) 1,2,4-triazole are the sole products formed after hydrolysis of **1–3**. In the presence of D-glucose (4 mol %) no other reaction products were formed as indicated by UV spectroscopy.

Kinetics. Pseudo-first-order rate constants, k_{obsd}, for the neutral hydrolysis of **1–3** under atmospheric pressure were measured at five different temperatures between 25 and 45 °C by monitoring the disappearance of **1** (at 273 nm) and **2** and **3** (at 225 nm) with a Varian Cary 210 or Perkin-Elmer lambda 5 spectrophotometer. All reactions were followed to completion. In a typical experiment, 10 μL of a stock solution in MeCN (containing 5×10^{-2} M of substrate) was added to 2.5 mL of the reaction medium in the cell. The rate constants were reproducible to within 1.5%. Isobaric activation parameters were obtained by using the Eyring equation (least-squares program). Errors in $\Delta^{\ddagger}H^{\ominus}$ and $\Delta^{\ddagger}S^{\ominus}$ were estimated from the standard deviation of the regression. In all cases $\Delta^{\ddagger}$Cp values were negligible, and correlation coefficients were better than 0.999. The volumes of activation for neutral hydrolysis of **1** were determined by using the method described previously.[16]

Transfer Parameters. Thermodynamic parameters for transfer of **5** from water to aqueous carbohydrate solutions were obtained from solubility measurements in the temperature range 15–45 °C. The experimental procedure has been described before.[31] Solubilities, calculated from the absorbance at 248 nm, were reproducible to within 6%.

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Notes

Stereoselective Reaction of Dithio-Substituted Crotylmetal with α-Oxy Carbonyl Compounds

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Diastereoselective reaction of crotylmetals with carbonyl compounds has been extensively investigated as a useful method in the synthesis of macrolide antibiotics and polyether ionophores.[2] In previous papers,[3] we have reported the regio- and stereochemistry regarding the reaction of (*E*)-2-(1-propen-1-yl)-1,3-dithiane (**1**) with various carbonyl compounds. In order to further exploit this method in organic synthesis, it is important to test the reactivity of α-oxy carbonyl compounds with the crotylmetal generated from **1**. We report here the result of reactions of (benzyloxy)acetaldehyde (**2**), D-glyceraldehyde acetonide (**3**) and ethyl pyruvate (**4**).

Results and Discussion

Metalation of the vinyl dithiane **1** was effected by treatment with *n*-BuLi in THF. The resulting crotyllithium was subsequently treated with (benzyloxy)acetaldehyde at −78 °C to give exclusively the γ-addition products of **5a** and **5s** in a ratio of 78:22 (Chart I). The predominance of the 3,4-anti adduct **5a** was predictable by considering a chair-like transition state (A) involving in the reaction.[2,3] While exclusive anti adduct was found in analogous reactions, e.g., with *n*-pentanal,[3] the increased syn adduct in this reaction with (benzyloxy)acetaldehyde might be attributed to a double chelate transition state (B, see below).

The reaction of **1** with D-glyceraldehyde acetonide under similar conditions afforded three γ-addition products, **6aa**, **6as**, and **6sa**, in a ratio of 44:43:13. The letter/s following the number of compounds indicates the stereochemistry at $C_{3,4}$ and $C_{4,5}$, i.e., **a** represents anti, while **s** represents syn configuration. The stereostructure of isomers of **6**

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