Consequences of the Preeminent Reactivity of 2-OH in Sucrose: Cyclic Acetalation at 2-OH and 3-OH under Basic Conditions

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The reaction of unprotected sucrose with *tert*-butyl chloromethyl ketone in dimethylformamide was investigated as a model for the study of the relative reactivity of the various hydroxy groups of sucrose. Besides the monoethers arising from the substitution of the chlorine atom by 2-OH and 1′-OH of sucrose, the major product is a *tert*-butyl hydroxymethyl 5-membered ring acetal involving 2-OH and 3-OH. The formation of this product illustrates the preeminent reactivity of 2-OH towards the carbonyl group of the α-chloromethyl ketone, leading to an intermediate hemiacetalic anion, which can enter by intramolecular acetal formation through an intermediate epoxide.

Introduction

The utilization of sucrose as an organic raw material requires the development of chemical transformations that are selective even when it is used as an unprotected polyol. This explains why the relative reactivity of hydroxy groups of carbohydrates, and particularly of sucrose, has been intensely studied in the past decades. Spectroscopic,[1−4] theoretical,[5−10] and chemical[11−13] studies have been conducted, providing a solid background for the understanding of the reactivity of unprotected sucrose. It has been shown that, depending on the nature of the electrophilic reagent, different selectivities can be observed. In some cases, the primary alcohols (6, 1′, 6′) are more reactive, notably for systems that are sensitive to steric hindrance. In the case of reversible reactions, such as esterification or alkyloxycarbonylation, the competitive migrations and/or cleavage make the links between the observed distribution of the products (thermodynamic) and the relative reactivity of the hydroxy groups (kinetic) more difficult to interpret. Presumably, the relative acidity of the OH groups of sucrose is responsible for the regioselectivity of some transformations. Notably, it is now established that the alcohol function at position 2 (on the glucosyl part) is the most acidic.[8,14−18]

In order to widen the scope of the nucleophilic behavior of unprotected sucrose, we examined its reaction with chloropinacolone (*tert*-butyl chloromethyl ketone) as a model for a more complex electrophilic species, in parallel with the known ability of chloroacetate to be grafted onto polysaccharides under basic conditions.[19,20] In the case of α-halo ketones, the carbonyl group is a real competitor as an electrophilic center, whereas the carboxylate of the chloroacetate is not. Chloropinacolone was chosen because it is an easy to handle, commercially available substrate having a *tert*-butyl residue that is chemically unreactive and thus does not interfere in the process.[21]

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Results and Discussion

The reaction was performed in anhydrous dimethylformamide using 2 equiv. of sucrose to 1 equiv. of chloropinacolone, as well as 2 equiv. of base (NaOH or K_2CO_3). At 80 °C, the newly formed products were monosubstituted sucrose derivatives, as determined by TLC analysis. Small amounts of higher substituted derivatives were formed subsequently. Three main products (**1a−3a**) were formed in a ca. 60% global yield, with all three having the same atomic composition (as shown by elemental analysis of their peracetylated derivatives **1b−3b**) and the same molecular ion, which corresponds to monosubstituted derivatives (Scheme 1).

Two products in the mixture (**2a** and **2b**) result from a Williamson etherification reaction, as proved by the typical NMR and IR patterns for the carboxymethyl linkage. Compounds **2a** and **3a** were identified as the sucrose monoethers substituted at O-2 and O-1′, respectively. The ^{13}C-NMR data for these isomers are reported in Table 1. A large downfield shift typical of ethers[22] was observed for the carbon atom directly involved in the etherification ($\Delta\delta$ = +8 ppm), as well as a notable upfield shift for the signals of the carbon atoms adjacent to the one bearing the substitution ($\Delta\delta$ = −2 ppm). The signals due to other parts of the molecule remain unchanged with the exception of the C-3′ signal. This can be explained by the fact that the hydrogen-bond network involving 2-OH, 1′-OH, and 3′-OH, is perturbed by substitution at 2-OH or 1′-OH. In the case of the peracetylated derivatives **2b** and **3b**, the etherified position led to changes similar to those observed for **2a** and **3a**. However, signals due to the α-carbon atoms were shifted downfield in this case. Confirmation of this identification was also provided by ^{1}H-NMR analysis, which showed that the etherified positions were not affected by the acetylation.

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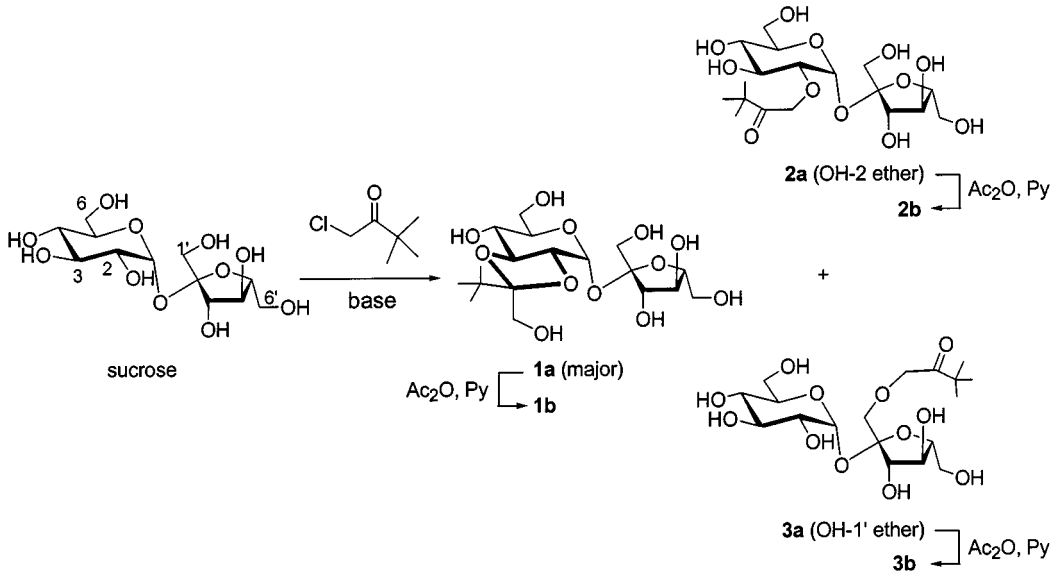


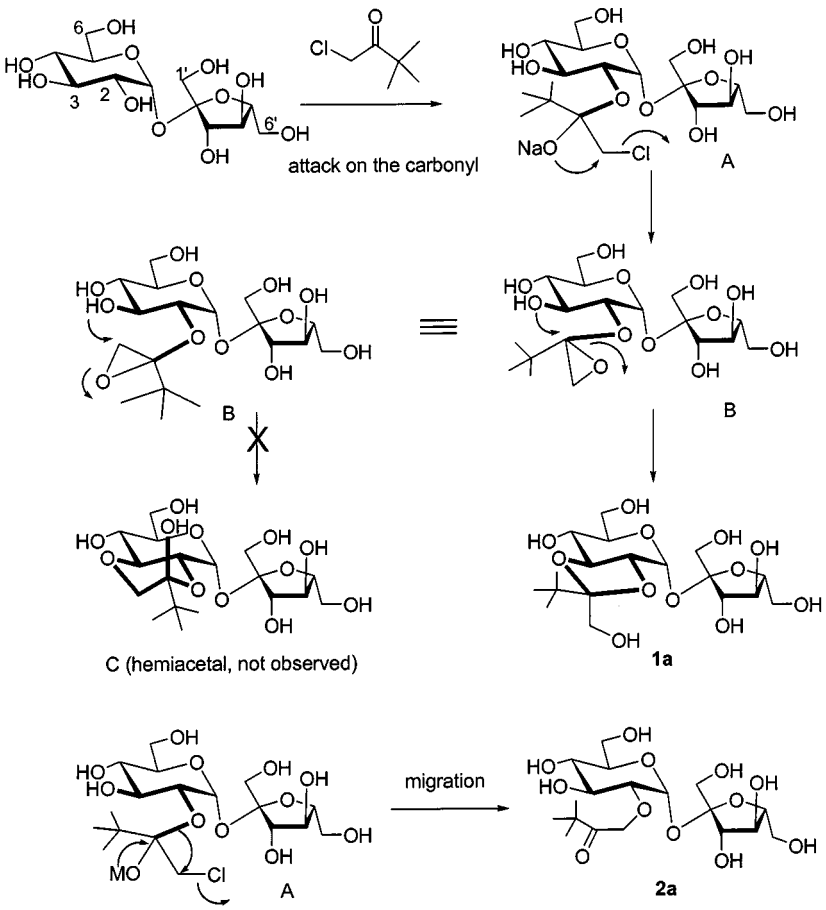
Scheme 1. Reaction of sucrose with *tert*-butyl chloromethyl ketone

Table 1. ^{13}C-NMR shifts for the products **1a**–**3a** (in [D$_6$]DMSO) and their peracetylated derivatives **1b**–**3b** (in $CDCl_3$) compared to sucrose or sucrose peracetate

	sucrose	**1a**	**2a**	**3a**	Ac_8-sucrose	**1b**	**2b**	**3b**
C-1	91.8	89.3	89.9	92.0	89.8	89.9	91.2	89.5
C-2	71.7	76.0	79.7	71.5	68.1	76.0	77.7	68.2
C-3	73.2	76.8	72.5	72.9	70.2	74.5	72.4	70.1
C-4	70.0	68.7	70.0	69.9	68.4	69.5	68.4	68.2
C-5	72.9	75.3	72.5	72.8	69.5	70.7	68.3	69.8
C-6	60.6	59.5	60.2	60.5	61.9	62.1	62.1	61.7
C-1′	62.0	61.6	61.4	70.2	62.8	64.1	63.4	71.1
C-2′	104.1	104.3	104.2	103.5	103.9	103.0	103.3	104.3
C-3′	77.1	76.0	75.9	76.3	75.6	75.3	75.1	75.4
C-4′	74.4	73.8	73.7	73.7	74.9	74.5	74.9	74.3
C-5′	82.6	82.6	82.5	82.3	79.0	78.5	78.5	78.3
C-6′	62.0	62.2	61.8	62.1	63.5	64.1	64.5	63.5
Me_3		25.5	25.9	25.8		25.2	26.1	26.2
C_{quat}		38.2	42.0	42.1		38.8	42.6	42.6
CH_2		62.2	71.8	72.2		62.6	72.1	72.3
CO		113.9	213.0	211.6		113.8	211.7	211.1

In the case of the major product **1a**, a peak corresponding to a carbonyl group was not present in the ^{13}C-NMR nor in the IR spectra. Furthermore, the signals for the other two carbon atoms arising from the pinacolone residue were shifted upfield compared to the "normal" ethers. This fact led us to believe that two hydroxy groups of the sucrose molecule were involved in the structural modification of **1a**, although only one pinacolone molecule was incorporated (Table 1). However, seven acetates were grafted onto the molecule upon peracetylation, revealing the presence of a new OH group. Besides the Favorskii rearrangement, which cannot occur in this case, an alternative outcome is the nucleophilic attack on the carbonyl group instead of the α-halo carbon atom. In addition, a new quatenary carbon atom was present as shown by the signal at δ = 113, which could correspond to an acetalic or hemiacetalic function. This could be the result of a subsequent cyclisation after a simple etherification reaction. Mechanisms leading to both of these linkages, depicted in Scheme 2, can be envisaged.

Based on the changes in the shifts of the carbon atoms of the sucrose backbone, as well as the effect on the proton shifts after acetylation, 2-OH and 3-OH were both involved in this linkage. The full determination of the structure was based on 500-MHz ^{1}H- and 2-D-CH-TOCSY and ^{1}H-COSY and NOESY NMR analysis of both the unprotected (**1a**) and the peracetylated (**1b**) compounds. A key element was the assignment of the correct pattern to each of the four CH_2 groups, which determined that the new CH_2 group was a primary alcohol (as in the acetal **1a**) and not an endocyclic methylene group (as in the hemiacetalic structure C). In the acetylated derivative **1b**, the chemical shift of C-1′ is distinctively higher than those of the three other methylene groups and, among these three, two are ABX systems corresponding to C-6 and C-6′. The remaining methylene group gives a more separated AB system. This peculiarity allowed us to distinguish this carbon atom from $CH_2$1′-OH in the spectrum of the unprotected compound **1a**. The position of the hydroxy groups in the ^{1}H-NMR spectrum in deuterated DMSO could thus be assigned for each position of the sucrose backbone, as well as for the fourth primary alcohol (after COSY analysis). The coupling between the methylene group arising from the pinacolone moiety and its OH group is the only one among the 4 primary OH groups to be a doublet of doublets rather than a triplet. This revealed a strong hindrance towards free rotation of this alcohol function, which could be connected with the dramatic shift of the signal of 3-OH to lower field. This is consistent with the position of the *tert*-butyl group, which is directed toward 2-H and 4-H as proved by the NOESY experiment. Effects of acetylation on the chemical shifts in the ^{1}H-NMR spectrum confirmed the identification of acetal **1a** as the major product of the reaction. Another clue lies in the chemical shift of the acetalic carbon



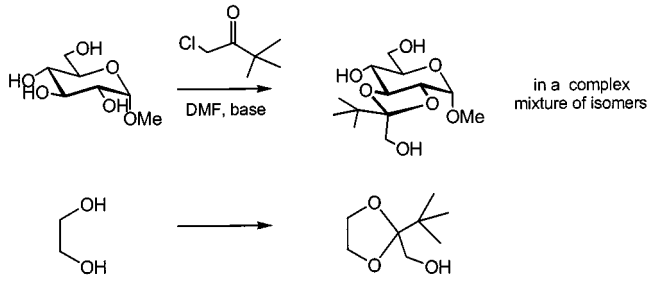
Scheme 2. Proposed mechanism for the formation of acetal **1a**

atom, which is typical for a five-membered ring acetal.[23][24] A reasonable path to lead to **1a** initially involves an attack of 2-OH on the carbonyl group to form an hemiacetalic alcoholate (A), which subsequently undergoes a fast cyclisation to the highly strained epoxide acetal B, followed by opening by 3-OH on the most electrophilic (acetalic) carbon atom (Scheme 2).[25–27] Since the acetal linkage is symmetrical, **1a** could also be the result of the attack of 3-OH on the carbonyl group of the chloropinacolone in the first step, but the absence of any other product reflecting the nucleophilicity of 3-OH makes this alternative less probable. A six-membered ring can also be formed, as was observed in the case of catechol derivatives or thiols. A hemiacetal (C) would thus be formed, but this structure was not detected in the mixture of products.[28] Another hypothesis involves a group migration (a possible mechanism in the chemistry of α-halo ketones), leading to the ether **2a**.

It has to be pointed out that the peculiar reactivity of 2-OH of sucrose is responsible for a more selective reaction compared to a simpler α-glucoside.[29] When starting from methyl α-D-glucoside, the reaction was much less straightforward. In this case, it was only possible to observe the typical peaks at $\delta \approx 114$, but the full identification of the products was not possible because of the complexity of the mixture. Ethylene glycol, when treated under the same conditions with chloropinacolone, also provided a similar linkage in low yield among other etherification products (Scheme 3). This reaction, leading to acetals from α-halomethyl ketones, has already been described in the literature[30] in the case of very reactive alcohols, but never in the case of sucrose. Moreover, the efficiency of the reaction was shown to decrease dramatically for less reactive alcohols.

In the case of sucrose, the other epimer at the acetalic linkage was not observed. The chiral α-hydroxy ketal is thus formed selectively and this might be a source of diastereoselectivity for further chemistry on the non-carbohydrate moiety. The chiral inductor can be cleaved smoothly by acid-catalyzed transacetalation (catalytic pyridinium *p*-toluenesulfonate in methanol) at room temperature. This treatment proceeds with only very limited cleavage of the glycosidic bond (detected through the formation of trace amounts of methyl glucosides) and therefore represents a way of directly selecting 2-OH and 3-OH of sucrose as a protecting sequence, providing complementary access to partially acetalated sucrose derivatives in addition to 4,6-acetals obtained by acid-catalyzed acetalations.[31–37]

A 2-fold excess of sucrose vs. chloropinacolone was used and limited amounts of disubstituted derivatives were obtained (quantified as a mixture of compounds after flash chromatography). The degree of substitution was estimated from the ^{1}H-NMR spectrum and confirmed by mass spec-



Scheme 3

trometry. The second substitution of acetal **1a** is favored because its concentration is higher compared to other isomers even though the more reactive OH is no longer available. As shown in Table 2, for a 4-fold excess, high conversion of the ketone (up to 80%) to monosubstituted derivatives was observed (which corresponds to a ca. 20% conversion of sucrose in acetal **1a**). The proportions of the three main products were measured (HPLC, NH_2 column) and showed that the formation of the acetal is favored compared to the Williamson-type ethers. Sodium hydroxide led to faster reactions compared to potassium carbonate. The proportion of compound **1a** increases under harsher conditions, probably because of a lower stability of ethers **2a** and **3a** due to their reactive carbonyl function.

On decreasing the temperature, more acetal was formed (Table 2) and the proportion of ether at 2-OH increased compared to that at 1′-OH, confirming again that reaction at 2-OH is kinetically favored. The mono/di ratio was not affected by the temperature change. For a given temperature, both ethers **2a** and **3a** were formed in the same relative amounts, reflecting a constant relative reactivity of 2-OH and 1′-OH with respect to the Williamson reaction. On the other hand, the attack on the carbonyl group is shown to be favored compared to that on the α-chloromethyl group. Since the ether at position 2 could also arise from an attack on the carbonyl group (see Scheme 2) through a migration pathway, it is also possible that its decrease in the mixture could be the result of an inhibition of this migration ability at lower temperature. The amount of ether at 1′-OH would therefore also decrease, but without an appropriately placed alcohol function the intermediate hemiketal or three-membered ring acetal would not develop towards an acetal linkage similar to the one observed in **1a**, and would be cleaved during the reaction treatment.

Water was used as an alternative solvent, but extensive hydrolysis of the chloromethyl ketone was observed, even starting from a concentrated sucrose solution (77% w/w). Low yields of sucrose derivatives were nevertheless obtained. The distribution of the regioisomers was found to be much more complex in this case. In the ^{1}H-NMR spectrum, peaks were observed at $\delta \approx 1.2$ and 0.95, which are typical values for *tert*-butyl residues next to a carbonyl group or an acetal linkage, respectively. However, the HPLC analysis of the mixture of "monosubstituted" derivatives proved that the acetal **1a** and the ether **2a** are still the major products in the mixture. This example is one more confirmation that, at least in a concentrated solution, solvation by water does not perturb the fundamental reactivity order of sucrose hydroxyl groups.[16,17,38,39]

Conclusion

The reactivity of unprotected sucrose with chloropinacolone in dimethylformamide under basic catalysis led to, as the major product, a cyclic hydroxymethyl alkyl acetal involving 2-OH and 3-OH, along with the Williamson ethers at 2-OH and 1′-OH. The hydroxy group at position 2 is confirmed to be the most reactive alcohol function among the eight present in the sucrose molecule. The kinetically favored pathway involves attack on the carbonyl group by the α-halo ketone, which finally led to the cyclic acetal that is likely to be formed via a three-membered ring acetal intermediate. This reaction provides an access to the direct selection of 2-OH and 3-OH of sucrose in a unique step.

Table 2. Yields and proportions of the products obtained by reaction of sucrose with chloropinacolone under various conditions[a]

	sucrose/ ketone	solvent	base [equiv.]	T [°C]	t [h]	**1a** [%][b,c]	**2a** [%][b,c]	**3a** [%][b,c]	mono [%][d]	di [%][d]	global yield [%][d]
1	2	DMF	NaOH (2.5)	80	1	31 (49)	22 (35)	10 (16)	63	19	82
2	2	DMF	NaOH (2.5)	80	3	31 (49)	22 (34)	11 (17)	64	27	91
3	2	DMF	K_2CO_3 (2)	80	1	20 (46)	16 (37)	8 (17)	44	9	53
4	2	DMF	K_2CO_3 (2)	80	24	29 (49)	21 (35)	9 (16)	59	27	86
5	4	DMF	NaOH (2.5)	80	3	45 (59)	22 (28)	10 (13)	77	21	98
6	4	DMF	K_2CO_3 (2)	80	3	40 (50)	29 (35)	12 (15)	81	17	98
7	2	DMF	NaOH (4)	45	1[e]	(61)	(27)	(12)			
8	2	DMF	NaOH (2.5)	45	48	34 (67)	11 (23)	5 (10)	50	20	70
9	2	DMF	K_2CO_3 (2)	60	1[e]	(57)	(27)	(16)			
10	2	DMF	K_2CO_3 (2)	45	1[e]	(64)	(25)	(11)			
11	2	DMF	K_2CO_3 (2)	45	48	25 (54)	15 (32)	6 (14)	46	14	60
12	2	H_2O[f]	NaOH	95	5	(24)	(23)	(13)	13	7	20
13	2	H_2O[f]	NaOH	95	24	(22)	(23)	(13)	10	6	16
14	2	H_2O[f]	NaOH	95	48	(26)	(22)	(13)	8	5	13

[a] Based on sucrose. – [b] Analytical yields (HPLC) after isolation of the fraction of monosubstituted derivatives by flash chromatography. – [c] Figures in parentheses indicate the relative proportions of **1a**, **2a**, and **3a**. – [d] Isolated yields based on the amount of starting ketone, after flash chromatography. – [e] Only the proportions were determined directly from the reaction mixture (HPLC). – [f] As a 77% aqueous solution of sucrose (w/w).

Experimental Section

General Procedure for the Reaction of Sucrose with Chloropinacolone in Organic Solvent: Sodium hydroxide (0.304 g, 7.6 mmol, 2.5 equiv.) or potassium carbonate (0.841 g, 6.09 mmol, 2 equiv.) was added to a stirred 9% w/w sucrose solution (2 g, 5.9 mmol) in anhydrous DMF (20 mL). *tert*-Butyl chloromethyl ketone (0.4 mL, 3.04 mmol, 1 equiv.) was added dropwise and the reaction was heated at 80°C. The reaction was monitored by TLC using a 56:20:20:4 mixture of dichloromethane/methanol/acetone/water as the eluent. After completion of the reaction, the mixture was cooled to room temperature and neutralized by adding 50% acetic acid in methanol. After evaporation of the solvent, flash chromatography (same solvent as for TLC) allowed isolation of the diethers (R_f = 0.62 to 0.79) and the monoethers (R_f = 0.27 to 0.48). The average substitution degree was determined by comparing the integrations for the alkyl chain and the sugar region in ^{1}H-NMR spectra ([D$_6$]DMSO). Monoethers could be further purified by semi-preparative HPLC (Nucleosil NH_2, 10 mm × 250 mm, 93/07 MeCN/H_2O, 6 mL/min, RI detection Shimadzu LC-6A) and identified by ^{1}H- and ^{13}C-NMR spectroscopy (Bruker). Analytical HPLC was performed using a Nucleosil NH_2 column (4.6 mm × 250 mm) eluted with a 90:10 MeCN/H_2O mixture at a 0.7 mL/min flow rate.

General Procedure for Peracetylation of the Monosubstituted Products: To a solution of monosubstituted product (300 mg, 0.68 mmol) in pyridine (2 mL), was added dropwise acetic anhydride (2 mL, 21 mmol) at 0°C, and the mixture stirred at room temperature during 24 h. The reaction was monitored by TLC using an 80:20 mixture of ether/hexane as the eluent. The solvent was evaporated under reduced pressure and the residue coevaporated several times with toluene. The residue was purified with the same eluent to obtain **1b**, **2b**, and **3b** (78, 80 and 74% yield, respectively).

Acetal 1a and Acetylated Acetal 1b. − Acetal 1a: ^{13}C NMR ([D$_6$]DMSO): δ = 113.8 (C acetalic), 104.3 (C-2′), 89.3 (C-1), 82.6 (C-5′), 76.8 (C-3), 76.0 (C-3′), 75.3 (C-2, C-5), 73.7 (C-4′), 68.7 (C-4), 62.2 (CH_2), 62.1 (C-6′), 61.6 (C-1′), 59.5 (C-6), 38.2 [*C*(CH$_3$)$_3$], 25.5 [C(*C*H$_3$)$_3$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 5.59 (d, J_{12} = 3.1 Hz, 1 H, 1-H), 4.29 (t, J_{34} = 9.7 Hz, 1 H, 3-H), 3.95 (t, $J_{3'4'}$ = 7.9 Hz, 1 H, 3′-H), 3.84−3.80 (q, 1 H, 4′-H), 3.65−3.52 (m, 7 H, 4-H, 6a,b-H, 5′-H, 6′a,b-H, 7a-H), 3.52−3.45 (m, 2 H, 5-H, 7b-H), 3.36−3.30 (m, 2 H, 1′a,b-H), 3.20−3.17 (q, J_{23} = 10.3 Hz, 1 H, 2-H), 0.96 [s, 9 H, C(CH$_3$)$_3$]. − IR: ṽ = 3361 cm^{-1}, 2976, 2884 γ(Csp^3−H) and γ(OH), 1492, 1407, 1312, 1153, 1115, 1054, 1000. − MS: FAB$^{[-]}$; *m/z*: 439 [M − H]$^-$, 179, 161, 143; FAB$^{[+]}$; *m/z*: 463 [M + Na]$^+$, 279, 261, 185, 163, 145, 127, 117. − **Acetylated Acetal 1b:** $C_{32}H_{46}O_{19}$ (734.701): calcd. C 52.31, H 6.31; found C 52.38, H 6.62. − [α]$_D^{21}$ = +31 (*c* = 0.8, MeOH). − ^{13}C NMR ([D$_6$]DMSO): δ = 170.7−169.4 (*C*OCH$_3$), 113.8 (C acetalic), 103.0 (C-2′), 90.0 (C-1), 78.5 (C-5′), 76.0 (C-2), 75.3 (C-3′), 74.5 (C-3, C-4′), 70.7 (C-5), 69.5 (C-4), 64.1 (C-1′, C-6′), 62.7 (CH_2), 62.0 (C-6), 38.8 [*C*(CH$_3$)$_3$], 25.2 [C(*C*H$_3$)$_3$], (COCH$_3$). − ^{1}H NMR ([D$_6$]DMSO): δ = 5.77 (d, J_{12} = 3.1 Hz, 1 H, 1-H), 5.44 (d, $J_{3'4'}$ = 7.3 Hz, 1 H, 3′-H), 5.41 (t, $J_{4'3'}$ = 7.3 Hz, $J_{4'5'}$ = 6.7 Hz, 1 H, 4′-H), 5.11 (t, J_{43} = 9.8 Hz, J_{45} = 9.77 Hz, 1 H, 4-H), 4.34−4.27 (m, $J_{6'a5'}$ = 7.3 Hz, $J_{6'b5'}$ = 4.9 Hz, J_{gem} = 12.2 Hz, 2 H, 6′a,b-H), 4.23−4.20 (m, 1 H, 5′-H), 4.24−4.21 (d, J_{7ba} = 12.8 Hz, 1 H, 7b-H), 4.22 (t, J_{23} = 9.8 Hz, J_{34} = 9.76 Hz, 1 H, 3-H), 4.19 (dd, $J_{1'ba}$ = 11.6 Hz, 1 H, 1′b-H), 4.17−4.11 (dd, J_{56} = 4.3 Hz, J_{6ab} = 12.2 Hz, 2 H, 6a,b-H), 3.97−3.92 (m, $J_{1'ab}$ = 11.2 Hz, J_{7ab} = 12.2 Hz, 3 H, 5-H, 1′a-H, 7a-H), 3.51 (q, J_{12} = 3.1, J_{23} = 9.77, 1 H, 2-H), 2.11−2.02 (m, 21 H, COCH$_3$), 0.96 [s, 9 H, C(CH$_3$)$_3$].

Ether 2a and Acetylated Ether 2b. − Ether 2a: ^{13}C NMR ([D$_6$]DMSO): δ = 213.9 (CO), 104.2 (C-2), 89.9 (C-1), 82.5 (C-5′), 79.7 (C-2), 75.9 (C-3′), 73.7 (C-4′), 72.5 (C-3, C-5), 71.8 (CH_2), 70.0 (C-4), 61.8 (C-6′), 61.4 (C-1′), 60.2 (C-6), 42.0 [*C*(CH$_3$)$_3$], 25.9 [C(*C*H$_3$)$_3$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 5.51 (d, J_{12} = 3.4 Hz, 1 H, 1-H), 4.65 (d, J_{gem} = 1.1 Hz, 2 H, CH_2), 3.95 (t, $J_{3'4'}$ = 8.5 Hz, 1 H, 3′-H), 3.79 (q, 1 H, 4′-H), 3.65−3.49 (m, 7 H, 5-H, 6a,b-H, 5′-H, 6′a,b-H, 3-H), 3.34 (s, 2 H, 1′a,b-H), 3.16 (t, J_{34} = 6.0 Hz, 1 H, 4-H), 2.94 (q, 1 H, 2-H), 1.08 [s, 9 H, C(CH$_3$)$_3$]. − IR: ṽ = 3359 cm^{-1}, 2937, 2515, 2343 γ(Csp^3−H) and γ(OH), 1726 γ(CO), 1476, 1382, 1164, 1070, 1015, 875 γ(C−OH) and δ(CH). − MS: FAB$^{[-]}$; *m/z*: 439 [M − H]$^-$, 341 [M − H − CH$_2$COC(CH$_3$)$_3$], 183, 129, 119; FAB$^{[+]}$; *m/z*: 463 [M + Na]$^+$, 301, 279, 261, 243, 185, 149, 127, 117. − **Acetylated Ether 2b:** $C_{32}H_{46}O_{19}$ (734.701): calcd. C 52.31, H 6.31; found C 52.66, H 6.46. − [α]$_D^{21}$ = +29 (*c* = 1.4, MeOH). − ^{13}C NMR ([D$_6$]DMSO): δ = 211.7 [*C*OC(CH$_3$)$_3$], 170.7−169.8 (*C*OCH$_3$), 103.3 (C-2′), 91.2 (C-1), 78.5 (C-5′), 77.7 (C-2), 75.1 (C-3′), 74.9 (C-4′), 72.4 (C-3), 72.0 (CH_2), 68.4 (C-5), 68.3 (C-4), 64.5 (C-6′), 63.4 (C-1′), 62.1 (C-6), 42.6 [CO*C*(CH$_3$)$_3$], 26.1 [COC(*C*H$_3$)$_3$], 20.7 (CO*C*H$_3$). − ^{1}H NMR ([D$_6$]DMSO): δ = 5.96 (d, J_{12} = 3.5 Hz, 1 H, 1-H), 5.55 (d, $J_{3'4'}$ = 7.3 Hz, 1 H, 3′-H), 5.42 (t, 1 H, 4′-H), 5.35 (t, J_{34} = 9.8 Hz, 1 H, 3-H), 4.92 (t, 1 H, 4-H), 4.52 (d, J_{gem} = 17.8 Hz, 1 H, 7a-H), 4.36 (d, 1 H, 7b-H), 4.37−4.09 (m, 8 H, 6a,b-H, 6′a,b-H, 1′a,b-H, 5-H, 5′-H), 3.36 (q, 1 H, 2-H), 2.08 (m, 21 H, COCH$_3$), 1.13 [s, 9 H, C(CH$_3$)$_3$].

Ether 3a and Acetylated Ether 3b. − Ether 3a: ^{13}C NMR ([D$_6$]DMSO): δ = 221.6 (CO), 103.5 (C-2′), 92.0 (C-1), 82.3 (C-5′), 76.3 (C-3′), 73.7 (C-4′), 72.9 (C-3), 72.8 (C-5), 72.2 (CH_2), 71.5 (C-2), 70.2 (C-1′), 69.9 (C-4), 62.1 (C-6′), 60.5 (C-6), 42.1 [*C*(CH$_3$)$_3$], 25.8 [C(*C*H$_3$)$_3$]. − ^{1}H NMR ([D$_6$]DMSO): δ = 5.17 (d, J_{12} = 3.7 Hz, 1 H, 1-H), 4.47 (d, J_{gem} = 6.5 Hz, 2 H, CH_2), 3.97 (t, $J_{3'4'}$ = 8.3 Hz, 1 H, 3′-H), 3.78 (m, 1 H, 4′-H), 3.61−3.46 (m, 6 H, 5-H, 5′-H, 6a,b-H, 6′a,b-H), 3.39 (m, 1 H, 3-H), 3.34 (s, 2 H, 1′a,b-H), 3.16−3.10 (m, 2 H, 2-H, 4-H), 1.07 [s, 9 H, C(CH$_3$)$_3$]. − IR: ṽ = 3687 cm^{-1}, 2937, 2492, 2343 γ(Csp^3−H) and γ(OH), 1726 γ(CO), 1664, 1468, 1375, 1156, 1078, 1015, 875 γ(C−OH) and δ(CH). − MS: FAB$^{[-]}$; *m/z*: 439 [M − H]$^-$, 341 [M − H − CH$_2$COC(CH$_3$)$_3$], 183, 129, 119; FAB$^{[+]}$; *m/z*: 463 [M + Na]$^+$, 301, 279, 261, 243, 185, 149, 127, 117. − **Acetylated Ether 3b:** $C_{32}H_{46}O_{19}$ (734.701): calcd. C 52.31, H 6.31; found C 52.57, H 6.45. − [α]$_D^{21}$ = +53 (*c* = 1.5, MeOH). − ^{13}C NMR ([D$_6$]DMSO): δ = 211.1 [*C*OC(CH$_3$)$_3$], 170.6−169.5 (*C*OCH$_3$), 104.3 (C-2′), 89.5 (C-1), 78.3 (C-5′), 75.4 (C-3′), 74.3 (C-4′), 72.3 (CH_2), 71.1 (C-1′), 70.1 (C-3), 69.8 (C-5), 68.2 (C-4, C-2), 63.5 (C-6′), 61.7 (C-6), 42.6 [CO*C*(CH$_3$)$_3$], 26.2 [COC(*C*H$_3$)$_3$], 20.6 (COCH$_3$). − ^{1}H NMR ([D$_6$]DMSO): δ = 5.73 (d, $J_{3'4'}$ = 7.0 Hz, 1 H, 3′-H), 5.71 (d, J_{12} = 3.8 Hz, 1 H, 1-H), 5.43 (t, 1 H, 4′-H), 5.43 (t, J_{34} = 9.1 Hz, 1 H, 3-H), 5.07 (t, 1 H, 4-H), 4.88 (q, 1 H, 2-H), 4.45 (d, $J_{7a,b}$ = 4.2 Hz, 2 H, 7a,b-H), 4.38−4.12 (m, 6 H, 6a,b-H, 6′a,b-H, 5-H, 5′-H), 3.58 (s, 2 H, 1′a,b-H), 2.18−2.01 (m, 21 H, COCH$_3$), 1.15 [s, 9 H, C(CH$_3$)$_3$].

Preparation of 2-(1,1-Dimethylethyl)-2-hydroxymethyl-1,3-dioxolane: To a solution of ethylene glycol (5 mL, 89 mmol) in anhydrous DMF (60 mL) were added chloropinacolone (3.3 mL, 18 mmol) and potassium carbonate (5 g, 36 mmol). No reaction occurred at room temperature. The mixture was heated at 80°C for 3 h. The mixture was cooled to room temperature, the insoluble salts were filtered off and a mixture of methanol and acetic acid (1:1, vol.) was added to the filtrate for neutralization. After evaporation of the solvent under reduced pressure, the residue was submitted to flash chromatography (hexane/ethyl acetate, 80:20). After 2 fractions (R_f = 0.9−0.7 and 0.7−0.45) containing notably *tert*-butyl hydroxymethyl ketone and disubstituted glycol derivatives, pure 2-

(1,1-dimethylethyl)-2-hydroxymethyl-1,3-dioxolane (R_f = 0.45) was obtained (475 mg, 16%). Some product was also present in the intermediate fraction. – ^{13}C NMR ([D$_6$]DMSO): δ = 113.7 (C acetalic), 66.8 (O–*C*H$_2$–*C*H$_2$–O), 63.9 (*C*H$_2$OH), 38.5 [*C*(CH$_3$)$_3$], 25.4 [C(*C*H$_3$)$_3$]. – ^{1}H NMR ([D$_6$]DMSO): δ = 3.91–4.11 (m, 4 H, O–C*H*$_2$–C*H*$_2$–O), 3.65 (d, *J* = 3.8 Hz, 2 H, C*H*$_2$OH), 2.05 (br. s, 1 H, O*H*), 1.16 [s, 9 H, C(C*H*$_3$)$_3$]. – IR: $\tilde{\nu}$ = 3289 cm^{-1}, 2968, 2965, 2906 γ(Csp^3–H) and γ(OH), 1500, 1375, 1187, 1078, 898, 671 γ(C–OH) and δ(CH).

Reaction of Chloropinacolone and Sucrose in Basic Aqueous Medium: To a stirred solution of sucrose (10 g, 29.3 mmol) in water (3 mL) were added sodium hydroxide (1.18 g, 29.6 mmol) and chloropinacolone (2 mL, 15.2 mmol). The viscous mixture was heated at 95°C and samples were taken and analyzed by HPLC. After 5 h, the mixture was neutralized by addition of acetic acid in methanol and the solvent was evaporated. Flash chromatography of the residue (CH_2Cl_2/acetone/methanol/water, 56:20:20:4) afforded, in order of elution, disubstituted sucrose derivatives (305 mg, 7%) and monosubstituted derivatives (855 mg, 13%), which were further analyzed by ^{1}H-NMR spectroscopy and HPLC.

Cleavage of Acetal 1a: A solution of acetal **1a** (95.8 mg, 0.22 mmol) in methanol was stirred at room temperature in the presence of pyridinium *p*-toluenesulfonate (0.23 μmol) added as a 20 mM solution in methanol. After 1 h, sucrose was detected by TLC and identified by HPLC, and slowly precipitated out of the solution. When heated at 40°C for 2 d, sucrose was accumulated and trace amounts of methyl glycosides were also detected.

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