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Carbohydrate Research 261 (1994) 255–266

CARBOHYDRATE RESEARCH

Selective alkylations of 1,4:3,6-dianhydro-D-glucitol (isosorbide)

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Received October 15th, 1993; accepted March 16th, 1994

Abstract

Each of the two hydroxyl groups of isosorbide can be alkylated selectively, either by direct alkylation with benzyl chloride or allyl bromide according to the reaction conditions, or by a three-step procedure involving selective monoacetylation, alkylation with four different reagents, and finally deacetylation. Monobutyl and monomethyl derivatives from isosorbide are also described.

1. Introduction

Research of new chiral pools in asymmetric synthesis has gained widespread importance over the past few years [1–3].

1,4:3,6-Dianhydro-D-glucitol (isosorbide) is an important by-product of the starch industry obtained by dehydration of D-glucitol [4]. It is thermally stable up to 280°C, of low cost, and available in large quantities. Therefore, it could be a serious candidate in asymmetric synthesis as a chiral inductor or catalyst. Its structure (Fig. 1) shows two hydroxyl groups of different reactivity [5] since one is endo at C-5 (involved in internal H-bonding [6]) and the other is exo at C-2.

Previously, isosorbide and isomannide (1,4:3,6-dianhydro-D-mannitol; in which both hydroxyl groups are endo) have been used to modify hydrides such as $NaBH_4$

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SSDI 0008-6215(94)00107-Q

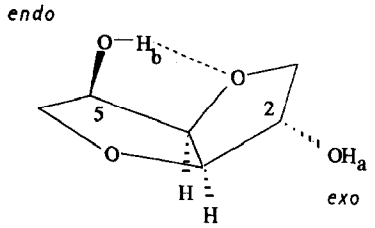


Fig. 1. Structure of 1,4:3,6-dianhydro-D-glucitol (isosorbide).

or $LiAlH_4$ in the asymmetric reduction of ketones [7,8]. Optical yields were at most 18%. Since it was claimed that monoalcohols are more efficient than diols [7,9], we decided to synthesize monoalcohols from isosorbide by alkylating selectively one of the two hydroxyl groups at C-2 or C-5. Only dialkylation has been reported in the literature [10–13] and regioselectivity has been demonstrated only in esterifications [14–16].

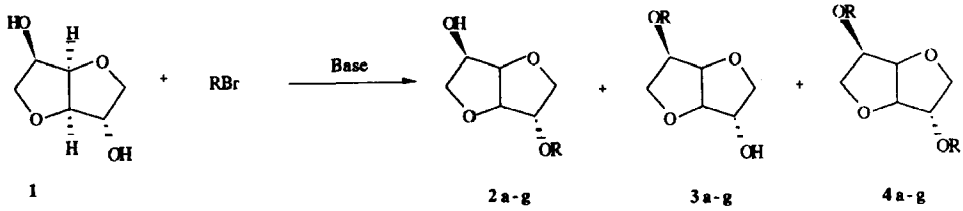
We therefore focused our research on the preparation of several new monoalkyl derivatives from isosorbide, with the introduction of the alkyl moiety either in the endo or exo position. For this purpose, we investigated two different routes from isosorbide **1**: (*A*) direct alkylation without protection of one hydroxyl group, and (*B*) selective *O*-monoacetylation [14–16] with subsequent alkylation and deacetylation.

We devoted special attention to the synthesis of monobenzyl ethers for two reasons: the benzyl moiety can be introduced as a protecting group for one of the two OH groups; the other OH group can then be alkylated, to afford functionalized monoalcohols after removal of the benzyl group by catalytic hydrogenation. The second reason concerns the aromaticity of the benzyl group which can lead to an improvement in optical yields in asymmetric synthesis on account of electrostatic interaction (such as π-stacking) between one reagent and the chiral substrate [17–19].

2. Results

(*A*) *Direct alkylations.*—(*i*) *Benzylation.* Benzylation of isosorbide (**1**) can lead to the formation (Scheme 1) of the 2-benzyl (exo), 5-benzyl (endo), and 2,5-dibenzyl ethers (**2a, 3a,** and **4a**) in ratios which depend on the experimental conditions.

The relative amounts of these compounds were studied as a function of the solvent and bases (Table 1). Temperatures and reaction times have also been optimized in each case. Best results were obtained with equivalent amounts of each reagent under the conditions indicated in Table 1. Yields reported were evaluated by GC with an internal standard and represent an average of several runs carried out under identical experimental conditions. They are based on amounts of isosorbide.



1 2a-g 3a-g 4a-g

a: R=Bn b: R=allyl c: R=Prop
d: R=Bu e: R=$CH_3(CH_2)_7$
f: R=$CH_3(CH_2)_9$ g: R=$CH_3(CH_2)_{11}$

Scheme 1.

In initial studies, several solvents were tested using NaOH as the base. Mixtures of products **2a, 3a**, and **4a** were obtained. As a result, Me_2SO and DMF were selected for subsequent studies due to the yield and their propensity to favour the endo product. Water was chosen as the best solvent for the exo compound.

The influence of several bases was studied in Me_2SO, DMF, and water at 90°C for 18 h. In some cases, we have investigated the addition of LiCl since it was shown that salt effects can affect both reactivity and selectivity [20].

The most important features from Table 1 are: (*a*) the influence of the counter-cation in Me_2SO where the smaller metallic cation leads to better endo selectivity ($Li^+ > Na^+ > K^+ > Cs^+$), whereas this influence is nonexistent in H_2O;

Table 1
Solvent and base effect [a]

Solvent	Base	**2a** (%)	**3a** (%)	**4a** (%)	Yield [b] (%)	Run
Me_2SO	LiH	6	40	13	59	4
	LiH + LiCl	0	63	11	74	5
	LiOH	3	40	3	46	6
	LiOH + LiCl	2	55	5	62	7
	NaOH	14	20	19	53	8
	KOH	22	17	15	54	9
	CsOH	25	15	19	59	10
	LiO^{t}Bu + LiCl	0	56	9	65	11
	LiOMe + LiCl	1	51	6	58	12
DMF	LiH	2	32	6	40	13
	LiH + LiCl	2	50	0	52	14
	LiH/Ultrasound	5	60	15	80	15
H_2O	LiOH	32	17	6	55	16
	NaOH	30	15	6	51	17
	KOH	30	10	3	43	18
	CsOH	40	15	4	59	19

[a] **1** + BnCl + base(1:1:1), 18 h, 90°C, 5 mmol in 3 mL of solvent.
[b] Isolated products.

(*b*) the positive effect of LiCl addition (runs 7, 11, 12, 14) which favours endo selectivity; (*c*) the beneficial effect of ultrasound (run 15) in a heterogeneous medium [21] instead of mechanical stirring.

In conclusion, we have achieved the regioselective synthesis of both monobenzyl ethers of isosorbide. 5-*O*-Benzylisosorbide (**3a**) (endo) can be obtained in up to 60% yield in Me_2SO with one equivalent of benzyl chloride and one equivalent of lithiated base (with one equivalent of LiCl in the case of LiOH or LiH) at 90°C for 22 h. DMF can also be used as solvent with one equivalent of LiH under ultrasound irradiation at 50°C for 22 h. The 2-benzyl ether **2a** (exo) is obtained mainly (with lower yields: 30 to 40%) in water by refluxing with one equivalent of alkali metal hydroxide for 9 h at 90°C.

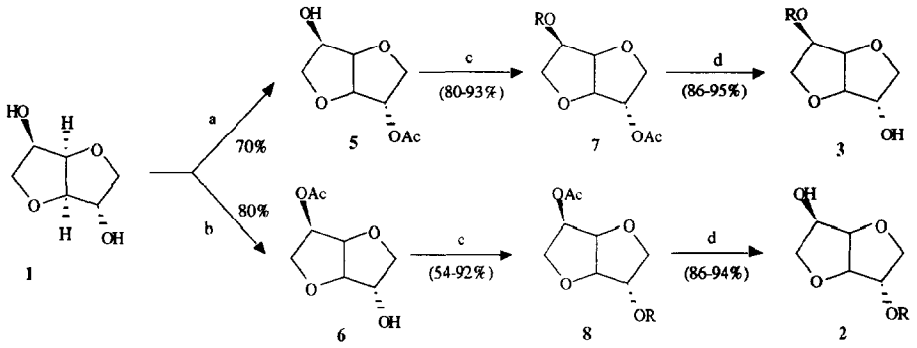
(*ii*) *Other alkylations.* In order to generalize the method, we studied the behaviour of other alkylating agents including allylic and linear aliphatic halides.

The results of allylation (Table 2) show results rather similar to those obtained for benzylation, best selectivities being obtained with LiOH–Me_2SO for the endo product and NaOH–H_2O for the exo one.

Table 2
Allylation [a] of isosorbide (**1**)

System	**2b** (%)	**3b** (%)	**4b** (%)	Yield [d] (%)
Me_2SO–LiOH [b]	3	69	6	78
DMF–LiH–ultrasound [c]	2	52	5	59
H_2O–NaOH [b]	35	15	6	56

[a] 1 + All-Br + base (1:1:1), 18 h, *T*°C, 5 mmol, in 5 mL of solvent. [b] 90°C. [c] 50°C. [d] Isolated products.



a: Ac_2O, 120-140°C, 1h then KOH, distillation b: Ac_2O, PbO, r.t, 20h

c: RX, Ag_2O, 2 days d: KOH, EtOH, 30°C, 0.5 h, then HCl

7a,3a : R=Bn **7b,3b : R=allyl** **7d,3d : R=Bu** **7h,3h : R=Me**
8a,2a : R=Bn **8b,2b : R=allyl** **8d,2d : R=Bu** **8h,2h : R=Me**

Scheme 2.

Table 3
Yields (%) of isolated products in alkylation and subsequent deacetylation of the isosorbide monoacetates **5** and **6**

RX	5 → 7	7 → 3	6 → 8	8 → 2
CH_3I	92	86	92	94
BnBr	85	95	88	86
AllBr	93	91	90	93
n-BuI	80	87	54	89

Some studies of other alkylations were performed with linear alkyl bromides by using the same sonicated LiH–DMF system during 48 h at 50°C. Relative proportions of the two isomers (endo- and exo-alkylated products) remained nearly the same [**3**:**2** ≥ 90:10] whatever the different R groups employed (cf. **c–g** in Scheme 1). In each case, high selectivities were obtained, but reactions were much slower than for allylation or benzylation of isosorbide (reaction times greater than 48 h).

Unfortunately, attempts to obtain the exo products **2c–g**, using NaOH in H_2O with the corresponding alkyl bromides, failed because of immiscibility.

(*B*) *Monoacetylation route.*—Isosorbide can be selectively monoacetylated [14–16] at the exo position, leading to **5**, or the endo position, giving **6** (Scheme 2).

The free hydroxyl group of **5** and **6** was alkylated using silver oxide in freshly distilled alkyl halides acting both as electrophile and solvent; this basic system is necessary here to avoid reaction with the acetylated moiety [22]. The *O*-acetyl ethers (**7** and **8**) thus obtained were purified by flash chromatography or distillation in good yields (54–93%) and subsequently *O*-deacetylated by treatment with KOH in EtOH. The monoethers of isosorbide were both obtained in chemically pure forms in high overall yields. Yields of all steps are reported in Table 3.

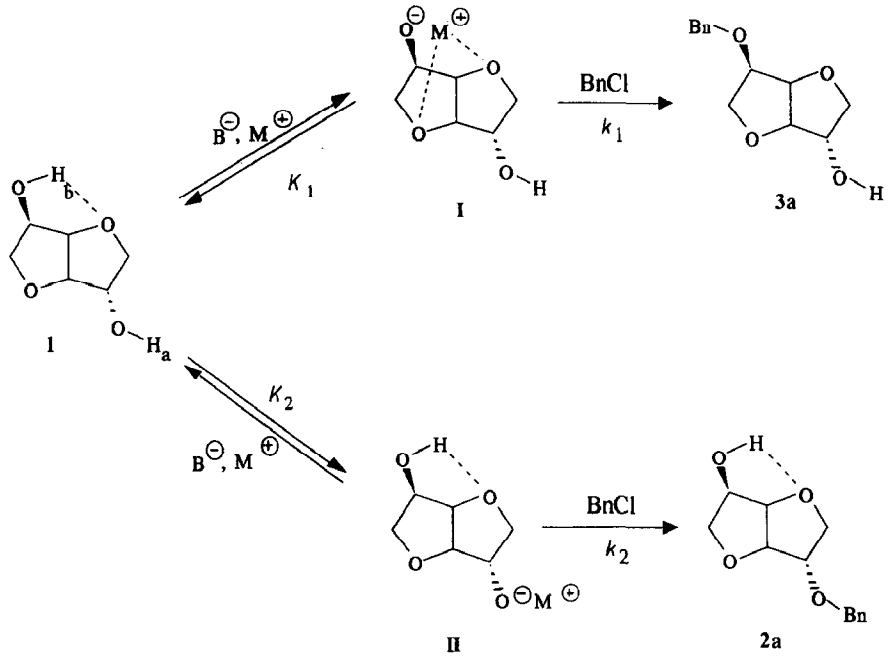
This three-step procedure provides an alternative to the direct alkylation route. It constitutes a more general access to all exo and endo monoalkylated products from isosorbide.

3. Discussion

In order to account for the different phenomenona observed, we propose some hypotheses and put forward two possible mechanisms.

(*1*) *In Me_2SO and DMF.*—First, we assumed that, under these conditions, ion pairs can be involved, for several reasons: (*a*) high concentrations of reagents (2 mol/L for each product); (*b*) high temperatures (especially in Me_2SO at 100°C) which lessen the dielectric constant of the solvent, making it less dissociative [23]; (*c*) hardness of ions (RO^- and Li^+), which promotes strong electrostatic interactions.

The base which reacts in Me_2SO is the dimsyl anion, obtained from deprotonation of Me_2SO with a strong base, and characterized by the brown colour of the



Scheme 3.

mixture. This fact explains why, in this solvent, the basic anion (hydroxide, alkoxide, hydride) has no effect on reaction selectivity, as we observed in Table 1.

We thus propose a mechanism which is illustrated in Scheme 3. So, it was possible to explain the selectivity observed above by evoking three contributions.

(*a*) A greater acidity of H_b (which is more easily removed and leads to intermediate **I**) according to ^1H NMR spectra of isosorbide and its monobenzylated compounds in Me_2SO-d_6 which showed that the chemical shift of the proton at C-5 [endo: $\delta(H_b) = 5.1$ ppm] is downfield of that at C-2 [exo: $\delta(H_a) = 4.7$ ppm]. Such complexation has already been postulated in alkylations of a lactoside [24] or with derivatives of ribose [25]. Unexpected selectivities were obtained in every case, on account of the formation of this kind of intermediate.

(*b*) A stabilization of intermediate **I** compared to intermediate **II** by chelation, and especially if the metallic cation is small enough (e.g., Li^+).

(*c*) A greater reactivity of intermediate **I** because the ion pair in **I** is looser than in intermediate **II**. So, intermediate **I** is probably formed mainly and is also the most reactive species. In these conditions, we should obtain preferentially the endo-benzylation product.

Finally, another effect can intervene due to the use of a lithium salt: Li^+ could have a specific interaction with the more basic oxygen of isosorbide (oxygen at the endo position because the O–H bond is the weakest). Therefore, on account of a proximity effect, the base linked to lithium could remove the proton H_b more

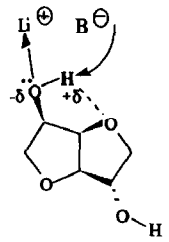


Fig. 2. Endo-benzylated compound 3.

easily and lead to the same intermediate **I** as above, which gives the endo-benzylated compound **3a** (Fig. 2).

(2) *In H_2O.*—Water is a solvent much more dissociative than Me_2SO ($\varepsilon \simeq 80$ for H_2O and $\varepsilon \simeq 46$ for Me_2SO at 25°C). Thus, there is formation of alkoxide ions solvated by water, and the internal hydrogen bond is removed. The two hydroxyl groups are chemically equivalent, but they remain sterically different and consequently distinct in reactivity.

Steric hindrance being less on the exo side, the proton at HO-2 is more easily removed by the base. Therefore, the exo OH group reacts more rapidly, as previously observed in acylation under phase transfer conditions where isosorbide is also dissolved in water [6].

Here, the reaction is performed under kinetic control and gives the product which is the more quickly formed (the exo-benzylated product).

4. Conclusion

We propose here two distinct routes for exo or endo monoalkylated isosorbide synthesis.

(*a*) An original direct alkylation leading to endo derivatives in satisfactory yields (> 60%) by achievement of the reaction in DMF or in Me_2SO, using lithiated bases eventually in the presence of LiCl (LiH + LiCl–Me_2SO) or under ultrasonic irradiation (LiH–US–DMF). Exo products can be selectively obtained in lower yields (40%) using hydroxides in H_2O with benzyl or allyl halides.

(*b*) Taking advantage of the regioselective monoacetylation of isosorbide in endo or exo positions, all the exo and endo monoethers can be obtained in good overall yields (30–70%) in a three-step procedure.

These new chiral monoethers derived from isosorbide can be used to obtain new monofunctionalized derivatives of isosorbide of interest in asymmetric synthesis. Work in this area is in progress to obtain new chiral ether alcohols or amino alcohols [26] which can be tested as new chiral auxiliaries or catalysts in asymmetric reactions [27].

5. Experimental

GC analyses were performed on a Carlo–Erba 2900 chromatograph with flame ionization and a capillary column Carbowax 15 m or OV1 10 m (carrier gas He at 0.5 bar). Internal standards for calibration in GC were dibutyl phthalate (Carbowax) and ethyl palmitate (OV1). ^1H and ^{13}C NMR spectra were recorded on a Brüker 200-MHz spectrometer for solutions in $CDCl_3$ or in Me_2SO-d_6. Optical rotations were measured on a Polartronic E polarimeter, using a 1-dm cell. Every product was analyzed by mass spectrometry with chemical ionization with NH_3 and gave the expected molecular ion peak.

General procedure for the alkylation of monoacetates of isosorbide.—To a solution of **5** or **6** (0.104 mol, 20 g), prepared from isosorbide by a literature procedure [14–16], in freshly distilled alkyl halide (200 mL) were added Ag_2O (0.138 mol, 31.7 g) and $CaSO_4$ (80 g). The resulting suspension was stirred for 2 days in the dark at room temperature, then diluted with ether (500 mL), filtered through Celite, and concentrated. For butyl iodide, the reaction was carried out in refluxing THF (200 mL) with only 20 mL of butyl iodide for 3 days.

General spectroscopic data for compounds **7** *and* **8**.—The following data were found for compounds **7h** and **8h**, but are the same for every other compound **7** and **8**.

Compounds **7**. ^1H NMR ($CDCl_3$): δ 3.6 (dd, 1 H, $J_{6a,5}$ 6.1, $J_{6a,6b}$ 10.3 Hz, H-6a), 3.9–4.15 (m, 4 H, H-1a,1b,5,6b), 4.52 (d, 1 H, $J_{3,4}$ 4.3 Hz, H-3), 4.70 (dd, 1 H, $J_{4,5}$ 4.5 Hz, H-4), 5.15 (dd, 1 H, $J_{2,1a}$ 1.0, $J_{2,1b}$ 3.0 Hz, H-2); ^{13}C NMR ($CDCl_3$): δ 69.9, 73.6, 78.4, 80.1, 85.8; IR (neat): ν_{max} 1740, 1370, 1235, 1050 cm^{-1}.

Compounds **8**. ^1H NMR ($CDCl_3$): δ 3.74 (dd, 1 H, $J_{6a,5}$ 5.7, $J_{6a,6b}$ 9.7 Hz, H-6a), 3.83–4.03 (m, 4 H, H-1a,1b,5,6b), 4.46 (d, 1 H, $J_{3,4}$ 4.6 Hz, H-3), 4.76 (dd, 1 H, $J_{4,5}$ 4.9 Hz, H-4), 5.14 (dd, 1 H, $J_{2,1a}$ 1.0, $J_{2,1b}$ 3.0 Hz, H-2); ^{13}C NMR ($CDCl_3$): δ 69.7, 72.7, 73.9, 80.3, 85.2, 85.5; IR (neat): ν_{max} 2940, 1740, 1460, 1370, 1241, 1095 cm^{-1}.

*2-O-Acetyl-1,4:3,6-dianhydro-5-O-benzyl-*D*-glucitol* (**7a**). The compound was purified by flash chromatography on silica gel with 1:1 EtOAc–hexane. Yield 85%; $[\alpha]_D^{27}$ + 127.1° (*c* 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.08 (s, 3 H, Ac), 7.29–7.42 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$): δ 20.7 (Ac), 127.8, 137.5, 169.8 (CO).

*2-O-Acetyl-5-O-allyl-1,4:3,6-dianhydro-*D*-glucitol* (**7b**). The compound was purified by bulb-to-bulb distillation. Yield 93%; bp 113–115°C (2 mmHg); $[\alpha]_D^{27}$ + 128.0° (*c* 0.60, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.05 (s, 3 H, Ac), 5.14–5.34 (m, CH_2 allyl), 5.83–6.02 (m, 1 H, CH allyl); ^{13}C NMR ($CDCl_3$): δ 20.7 (Ac), 79.2, 117.6, 134.3, 169.8 (CO).

*2-O-Acetyl-1,4:3,6-dianhydro-5-O-butyl-*D*-glucitol* (**7d**). The compound was purified by flash chromatography on silica gel with 1:1 EtOAc–hexane. Yield 80%; $[\alpha]_D^{27}$ + 110.4° (*c* 0.58, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.91 (t, 3 H, CH_3), 1.37 (m, 2 H, CH_2), 1.57 (m, 2 H, CH_2), 2.06 (s, 3 H, Ac); ^{13}C NMR ($CDCl_3$): δ 13.7, 19.0, 20.7 (Ac), 31.7, 169.8 (CO).

*2-O-Acetyl-1,4:3,6-dianhydro-5-O-methyl-*D*-glucitol* (**7h**). The compound was purified by flash chromatography on silica gel with 1:1 EtOAc–hexane. Yield 92%; $[\alpha]_D^{27}$ + 113.1° (*c* 0.78, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.07 (s, 3 H, Ac), 3.47 (s, 3 H,

OCH_3); ^{13}C NMR ($CDCl_3$): δ 20.8 (Ac), 58.1 (OCH_3), 169.8 (CO). Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.39; H, 7.26.

5-O-Acetyl-1,4:3,6-dianhydro-2-O-benzyl-D-glucitol (**8a**). The compound was purified by bulb-to-bulb distillation. Yield 88%; bp 140°C (2 mmHg); $[\alpha]_D^{27}$ + 82.7° (*c* 0.87, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.12 (s, 3 H, Ac), 7.29–7.36 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$): δ 20.5 (Ac), 71.3, 127.5, 127.7, 128.3, 137.4, 170.2 (CO).

5-O-Acetyl-2-O-allyl-1,4:3,6-dianhydro-D-glucitol (**8b**). The compound was purified by bulb-to-bulb distillation. Yield 90%; bp 110°C (2 mmHg); $[\alpha]_D^{27}$ + 90.6° (*c* 0.77, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.11 (s, 3 H, Ac), 3.90–4.04 (OCH_2), 5.09–5.33 (CH_2 allyl), 5.81–5.98 (CH allyl); ^{13}C NMR ($CDCl_3$): δ 20.5 (Ac), 70.2, 117.3, 133.9, 170.2 (CO).

5-O-Acetyl-1,4:3,6-dianhydro-2-O-butyl-D-glucitol (**8d**). The compound was purified by flash chromatography on silica gel with 1:1 EtOAc–hexane. Yield 54%; $[\alpha]_D^{27}$ + 61.5° (*c* 0.91, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 0.89 (t, 3 H, CH_3), 1.25–1.60 (m, 4 H, 2 CH_2), 2.10 (s, 3 H, Ac), 3.46 (t, 2 H, OCH_2); ^{13}C NMR ($CDCl_3$): δ 13.6, 19.1, 20.5 (Ac), 31.6, 170.2 (CO).

5-O-Acetyl-1,4:3,6-dianhydro-2-O-methyl-D-glucitol (**8h**). The compound was purified by bulb-to-bulb distillation. Yield 92%; bp 90–92°C (2 mmHg); $[\alpha]_D^{27}$ + 97.6° (*c* 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.11 (s, 3 H, Ac), 3.37 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$): δ20.5 (Ac), 56.9 (OCH_3), 170.2 (CO). Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.37; H, 7.06.

General procedure for the direct synthesis of benzylated compounds **2a, 3a**, *and* **4a** *from isosorbide.*—As a typical procedure, the reaction conditions are described for run 6 of Table 1. Isosorbide (18.25 g, 125 mmol) and $LiOH \cdot H_2O$ (5.25 g, 125 mmol) were dissolved at 90°C in Me_2SO (60 mL), followed 20 min later by dropwise addition of benzyl chloride (14.4 mL, 125 mmol). The solution was stirred for 18 h, then acidified to pH 1 with 2 M HCl and extracted by EtOAc. The organic layer was dried over anhyd Na_2SO_4 and evaporated under reduced pressure. The residual Me_2SO was then evaporated under high vacuum. The residual oil was chromatographed on a silica gel column under pressure and eluted with hexane–EtOAc. The dibenzylated compound was eluted with 1:5 EtOAc–hexane. Exo and endo benzylated products were eluted with 1:1 EtOAc–hexane.

General procedure for the direct synthesis of allylated compounds **2b, 3b**, *and* **4b** *from isosorbide.*—Isosorbide (18.25 g, 125 mmol) and NaOH (5 g, 125 mmol) were dissolved in water (50 mL). Allyl bromide (10.8 mL, 125 mmol) was then added dropwise and the solution was stirred at 100°C for 9 h. The mixture was then acidified with 2 M HCl to pH 1 and products were extracted with EtOAc. The organic layer was dried over anhyd Na_2SO_4 and the solvent evaporated under vacuum. The residual oil was chromatographed on silica gel under pressure and eluted by pentane–EtOAc. The diallylated compound was eluted with 1:9 EtOAc–hexane, and the two other products were eluted with 3:7 EtOAc–hexane.

Synthesis of alkylated compounds **c, d, e, f**, *and* **g** *from isosorbide.*—The same procedure as for benzylation of isosorbide was used. The crude residual oil was analysed by GC (Table 4) and the major product identified by ^1H NMR spectra (by comparison of the integration of each OH peak). GC analyses were performed on

Table 4
GC Retention times (min) of alkylated products of isosorbide.

Product	$n = 2$ (c)	$n = 3$ (d)	$n = 7$ (e)	$n = 9$ (f)	$n = 11$ (g)
2 (exo)	4.0	5.1	7.3	11.4	13.5
3 (endo)	4.7	5.8	10.1	12.1	14.0
4 (di)	6.1	8.3	15.7	N.O.	N.O.

[a] N.O., Not observed.

OV1 15 m with the same gradient for each product: 80 to 280°C (10°C/min) then 280°C during 8 min.

General procedure for the synthesis of monoethers **2a, b, d, h** *and* **3a, b, d, h** *from acetoxy ethers* **7a, b, d, h** *and* **8a, b, d, h.**—To a solution of potassium hydroxide (5 g, 75 mmol) in ethanol (70 mL) was added **7** or **8** (50 mmol, 10 g). The mixture was stirred at 50°C for 30 min and then neutralized with 1 M HCl. After being concentrated, the crude product was extracted with EtOAc (5 × 50 mL). The combined extracts were dried over Na_2SO_4 and evaporated in vacuo. The ethers were purified by distillation under reduced pressure.

General spectroscopic data for compounds **2**, **3**, *and* **4**.—The following data were found for compounds **2h** and **3h**, but are the same for every other compound **2**, **3**, and **4**.

Compounds **2**. ^{1}H NMR ($CDCl_3$): δ 3.55 (dd, 1 H, $J_{6a,5}$ 6.1, $J_{6a,6b}$ 10.3 Hz, H-6a), 3.80–3.91 (m, 3 H, H-1a,2,6b), 4.03 (d, 1 H, $J_{2,1b}$ 3.0 Hz, H-1b), 4.27 (m, 1 H, H-5), 4.45 (d, 1 H, $J_{3,4}$ 4.5 Hz, H-3), 4.58 (dd, 1 H, $J_{4,5}$ 4.8 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 72.1, 72.8, 73.3, 81.5, 85.2, 85.4; IR (neat): ν_{max} 3430, 1115, 1010 cm^{-1}.

Compounds **3**. ^{1}H NMR ($CDCl_3$): δ 3.53 (dd, 1 H, $J_{6a,5}$ 5.7, $J_{6a,6b}$ 10.3 Hz, H-6a), 3.87–3.95 (m, 4 H, H-1a,1b,5,6b), 4.28 (m, 1 H, H-2), 4.43 (d, 1 H, $J_{3,4}$ 4.6 Hz, H-3), 4.61 (dd, 1 H, $J_{4,5}$ 4.9 Hz, H-4); ^{13}C NMR ($CDCl_3$): δ 69.6, 75.6, 76.2, 79.5, 81.5, 88.2; IR (neat): ν_{max} 3420, 1135, 1085, 1070, 1020, 980 cm^{-1}.

*1,4:3,6-Dianhydro-2-O-benzyl-*D*-glucitol* (**2a**). Yield: 94% from **8a**; bp 115°C (2 mmHg); mp 100–102°C; $[\alpha]_D^{27}$ + 27.6° (*c* 0.51, $CHCl_3$); GC: OV1 10 m: 80 to 230°C (10°C/min) t_R 7.0 min, Carbowax 15 m: 140°C (5 min) then 140 to 200 (6°C/min) t_R 5.36; ^{1}H NMR (Me_2SO-d_6): δ 4.80 (s, 1 H, OH); ($CDCl_3$): 2.74 (d, 1 H, OH), 7.30–7.38 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$): δ 71.4, 127.6, 127.6, 128.4, 137.3. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83, Found: C, 66.06; H, 6.87.

*2-O-Allyl-1,4:3,6-dianhydro-*D*-glucitol* (**2b**). Yield: 93% from **8b**; bp 100°C (2 mmHg); $[\alpha]_D^{27}$ + 31.0° (*c* 0.92, $CHCl_3$); GC: OV1 15 m: 110°C t_R 3.5 min; ^{1}H NMR (Me_2SO-d_6): δ 4.73 (s, 1 H, OH); ($CDCl_3$): δ 2.74 (d, 1 H, OH), 5.17–5.34 (CH_2 allyl), 5.82–6.00 (CH allyl); ^{13}C NMR ($CDCl_3$): δ 70.3, 117.4, 133.7.

*1,4:3,6-Dianhydro-2-O-butyl-*D*-glucitol* (**2d**). Yield: 89% from **8d**; bp 100–102°C (2 mmHg); $[\alpha]_D^{27}$ + 24.8° (*c* 0.68, $CHCl_3$); GC: OV1 15 m: 80 to 280°C (10°C/min) and then 280°C during 5 min t_R 5.1 min; ^{1}H NMR (Me_2SO-d_6): δ 4.75 (s, 1 H, OH); ($CDCl_3$): 0.90 (t, 3 H, CH_3), 1.18–1.61 (m, 4 H, CH_2), 2.78 (d, 1 H, OH), 3.44–3.66 (m, OCH_2); ^{13}C NMR ($CDCl_3$): δ 13.7, 19.1, 31.5, 69.4.

*1,4:3,6-Dianhydro-2-*O*-methyl-*D*-glucitol* (**2h**). Yield: 94% from **8h**; bp 120–122°C (13 mmHg); $[\alpha]_D^{27}$ + 22.3° (*c* 0.83, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.80 (d, 1 H, OH), 3.38 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$): δ 57.0 (OCH_3).

*1,4:3,6-Dianhydro-5-*O*-benzyl-*D*-glucitol* (**3a**). Yield: 95% from **7a**; bp 150°C (1.5 mmHg); mp 60–62°C; $[\alpha]_D^{27}$ + 121.2° (*c* 0.54, $CHCl_3$); GC: OV1 10 m: 80 to 230°C (10°C/min) t_R 7.7 min, Carbowax 15 m: 140°C (5 min) then 140 to 200 (6°C/min) t_R 8.9 min; ^{1}H NMR (Me_2SO-d_6): δ 5.2 (s, 1 H, OH); ($CDCl_3$): 2.62 (s, 1 H, OH), 7.29–7.40 (m, 5 H, phenyl); ^{13}C NMR ($CDCl_3$): δ 72.3, 127.6, 128.3, 137.5. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found C, 65.95; H, 6.69.

*1,4:3,6-Dianhydro-2,5-di-*O*-benzyl-*D*-glucitol* (**4a**). $[\alpha]_D^{27}$ + 71.1° (*c* 0.58, $CHCl_3$); GC: OV1 10 m: 80 to 230 (10°C/min) t_R 12.2 min, Carbowax 15 m: 140°C (5 min) then 140 to 200°C (6°C/min) t_R 16.9 min; ^{1}H NMR ($CDCl_3$): δ 4.55 (OCH_2), 7.20–7.4 (phenyl).

*5-*O*-Allyl-1,4:3,6-dianhydro-*D*-glucitol* (**3b**). Yield: 91% from **7b**; bp 110°C (0.1 mmHg); $[\alpha]_D^{25}$ + 92.1° (*c* 0.68, $CHCl_3$); GC: OV1 15 m: 110°C t_R 4.8 min; ^{1}H NMR: ($CDCl_3$): δ 2.65 (s, 1 H, OH), 3.92–4.43 (OCH_2), 5.17–5.35 (CH_2 allyl), 5.83–6.03 (CH allyl); ^{13}C NMR: ($CDCl_3$): δ 71.5 117.6, 134.3.

*2,5-Di-*O*-allyl-1,4:3,6-dianhydro-*D*-glucitol* (**4b**). $[\alpha]_D^{25}$ + 88° (*c* 0.60, $CHCl_3$); GC: OV1 15 m: 110°C t_R 9.3 min; ^{1}H NMR ($CDCl_3$): δ 3.80–4.1 (OCH_2), 5.15–5.37 (CH_2 allyl), 5.78–6 (CH allyl).

*1,4:3,6-Dianhydro-5-*O*-butyl-*D*-glucitol* (**3d**). Yield 87% from **7d**; bp 125–127°C (2 mmHg); $[\alpha]_D^{27}$ + 89.9° (*c* 0.70, $CHCl_3$); GC: OV1 15 m: 80 to 230°C (10°C/min) and then 280°C during 5 min t_R 5.8 min; ^{1}H NMR: ($CDCl_3$): δ 0.89 (t, 3 H, CH_3), 1.34 (m, 2 H, CH_2), 1.58 (m, 2 H, CH_2), 2.84 (s, 1 H, OH); ^{13}C NMR: ($CDCl_3$): δ 13.7, 19.0, 31.6, 76.5.

*1,4:3,6-Dianhydro-5-*O*-methyl-*D*-glucitol* (**3h**). Yield 86% from **7h**; bp 120–122°C (3 mmHg); $[\alpha]_D^{27}$ + 104.1° (*c* 0.75, $CHCl_3$); ^{1}H NMR: ($CDCl_3$): δ 2.73 (s, 1 H, OH), 3.46 (s, 3 H, OCH_3); ^{13}C NMR: ($CDCl_3$): δ 58.0. Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.29; H, 7.50.

Acknowledgments

We thank the French Society Roquette Frères (62136 Lestrem) and Dr. G. Flèche for financial support to part of this study. We are grateful to the French Ministry of Research and Technology (MRT) for a CIFRE grant to R. Tamion.

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