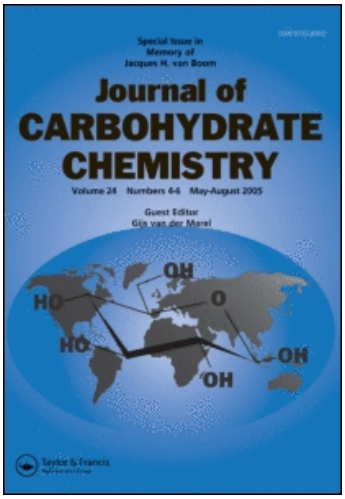



## Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

# One-Pot Synthesis of Substituted Allyl-α-d-Glucopyranosides by an *in situ* Anomerization Protocol

André B. Charette[a]; Nathalie Turcotte[a]; Bernard Côté[a]
[a] Département de Chimie, Université de Montréal, Montréal, Québec, Canada

**To cite this Article** Charette, André B. , Turcotte, Nathalie and Côté, Bernard(1994) 'One-Pot Synthesis of Substituted Allyl-α-d-Glucopyranosides by an *in situ* Anomerization Protocol', Journal of Carbohydrate Chemistry, 13: 3, 421 — 432
**To link to this Article: DOI:** 10.1080/07328309408009203
**URL:** http://dx.doi.org/10.1080/07328309408009203

J. CARBOHYDRATE CHEMISTRY, 13(3), 421-432 (1994)

# ONE-POT SYNTHESIS OF SUBSTITUTED ALLYL-α-D-GLUCOPYRANOSIDES BY AN *in situ* ANOMERIZATION PROTOCOL

André B. Charette,*[1] Nathalie Turcotte, and Bernard Côté

Département de Chimie, Université de Montréal, C.P. 6128,
Succ. A, Montréal, Québec CANADA H3C 3J7

*Received June 25, 1993 - Final Form December 21, 1993*

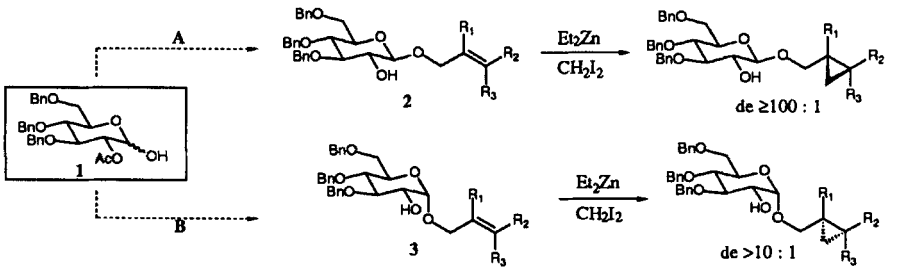


## ABSTRACT

A new 3-step, 1-pot procedure for the stereoselective α-glycosylation of substituted allylic alcohols has been developed. The key step involves an *in situ* anomerization of the β-glycoside, obtained by Schmidt's glycosylation method, upon treatment with $TiCl_4$.

## INTRODUCTION

We reported recently that the 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside unit is an efficient chiral auxiliary for the asymmetric cyclopropanation reaction.[2] It was also found that the corresponding α-D-glucopyranoside behaves as a "pseudo-mirror image" of the β-anomer.[3] Both enantiomers of a cyclopropylmethanol moiety are accessible from the same chiral auxiliary providing that the stereochemistry of the anomeric position can be controlled in the glycosylation reaction (Scheme 1).

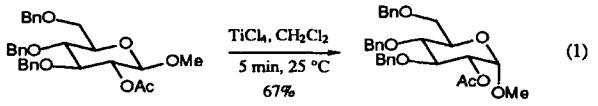



**Scheme 1**

In this paper, we wish to report a new approach to the stereoselective synthesis of **2** or **3** from the same precursor **1** as well as an improved synthesis of **1**.

## RESULTS AND DISCUSSION

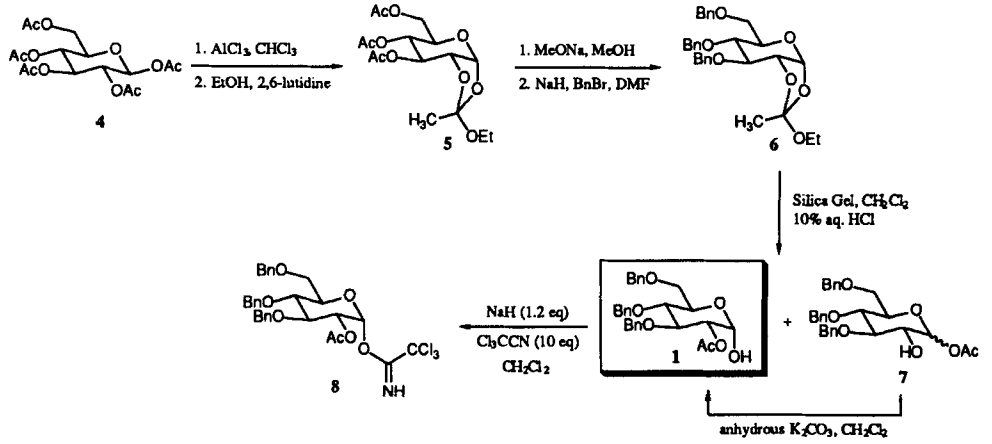
The anomerization reaction of glycosides is a well-known process.[4] Although Koto[5] and Nakanishi[6] reported recently that a number of alkyl 2-*O*-acetyl-β-D-glucopyranosides anomerized in good yields to the corresponding α-anomer upon treatment with $TiCl_4$ (eq 1) or $FeCl_3$, the clean anomerization of allyl 2-*O*-acetyl-β-D-glucopyranosides remained to be established.




(1)

It was believed that combination of Schmidt's trichloroacetimidate glycosylation method[7] and the anomerization reaction, followed by an *in situ* cleavage of the 2-acetyl group, would efficiently produce the desired allyl α-D-glycosides.

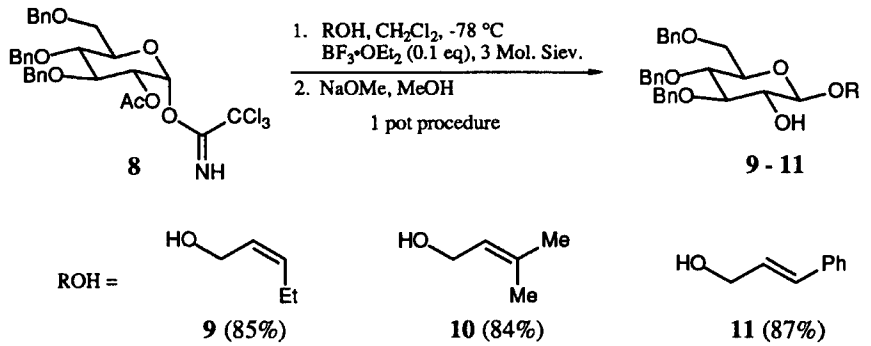
The synthesis of the precursor is illustrated in Scheme 2. β-D-Glucose pentaacetate was converted into orthoester **5**[8] upon treatment with $AlCl_3$ (4 h, 0 °C), EtOH and 2,6-lutidine (24 h, 25 °C, 66% overall yield, 10:1 mixture of orthoesters). After straightforward protecting group manipulations (81% overall), ortho ester **6**[9] was stirred over acidic silica gel in $CH_2Cl_2$ to produce, in quantitative yield, a 2:1 mixture of the undesired 1-acetyl derivative **7** and the desired lactol **1**.[10] It was found, however, that **1** was formed almost exclusively (>15:1) if the mixture was stirred in $CH_2Cl_2$ over anhydrous $K_2CO_3$ (24 h, 25 °C).




**Scheme 2**

Simple filtration and concentration of the solution produced lactol **1**[11] in 95% yield as a white solid. The overall synthesis of the chiral auxiliary is straightforward, efficient, and does not require any purification by chromatography. Lactol **1** was then converted to the desired glycosylation precursor **8** upon treatment with NaH in the presence of excess trichloroacetonitrile (78%, $CH_2Cl_2$, -50 to -20 °C).[11]

As expected, the β-selective glycosylation, under Schmidt's conditions, proceeded extremely well as shown in Scheme 3. A catalytic amount of $BF_3{\cdot}OEt_2$ was sufficient to induce glycosylation in very good yield even with β-glycosides derived from relatively sensitive allylic alcohols.

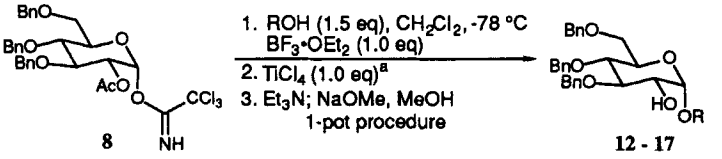


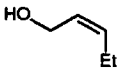
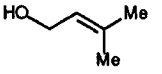
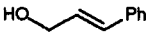
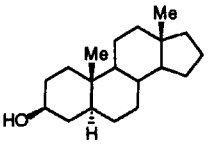

**Scheme 3**

Furthermore, subsequent addition of 10 eq of NaOMe (1.0 M in MeOH) cleanly cleaved the acetate group without need for isolation of the intermediate 2-*O*-acetyl-β-glycoside.

Initial studies of the glycosylation coupled with the *in situ* anomerization involved the use of 2 eq of $TiCl_4$ as the Lewis acid, trichloroacetimidate **8** and *cis*-2-penten-1-ol. Even though the major product was the desired α-anomer (with no trace of β by TLC), the yield for the overall process was relatively low due to competitive formation of the corresponding glycosyl chloride. It was found that sequential addition of 1 eq of $BF_3{\cdot}OEt_2$,[12] 1 eq of $TiCl_4$, and 10 eq of NaOMe produced the desired 1-*O*-allyl-α-D-glucopyranose in excellent yields. Representative examples are shown in Table 1. The reaction conditions are suitable to generate α-D-glucopyranosides of mono- and di-substituted allylic alcohols (entry 1,2). Trisubstituted allylic alcohols showed some decomposition under the anomerization conditions (entry 3). Nevertheless, it was found that higher yields of the α-glycoside were obtained if the anomerization was carried out on the pure, isolated β-glycoside. The highly acid labile cinnamyl β-glycoside completely decomposed when treated with $TiCl_4$. Furthermore, other milder Lewis Acids such as $TiCl_2(O\textit{i}\text{-}Pr)_2$ were ineffective at promoting the anomerization of this

**TABLE 1. One-pot synthesis of 3,4,6-tri-*O*-benzyl-α-D-glucopyranosides**




| Entry | ROH | Yield[b] |
|---|---|---|
| 1 |  | 93% (**12**) |
| 2 |  | 81% (**13**) |
| 3 |  | 9% (47%)[c] (**14**) |
| 4 |  | decomp.[d] (**15**) |
| 5 |  | 86% (**16**) |
| 6 |  | 58%[e] (**17**) |

a. Stirred at -78 °C for 15 min and at 0 °C for 1 h. b. Isolated yields of analytically pure α-anomer. In all cases the ratio α/β was shown to be >15:1 by $^1H$ NMR. c. The value in parentheses refers to the yield for the anomerization of pure β-anomer at -78 °C (90 min) followed by warming to 0 °C in $CH_2Cl_2$ for 30 min. d. Decomposition occurred under the anomerization conditions. e. 1.0 equivalent of the alcohol was used in this case.

substrate. On the other hand, saturated alcohols gave excellent yields of the α-glycosides (entry 5,6).

In summary, we have described a new and useful method for the synthesis of substituted allyl α-glycosides which are useful precursors for the stereoselective cyclopropanation reaction. Further studies to develop new conditions for the *in situ* anomerization of the most acid-sensitive substrates are in progress.

## EXPERIMENTAL

**General Methods and Materials.** Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Unless otherwise noted, all non-aqueous reactions were performed under an oxygen-free atmosphere of nitrogen or argon with rigid exclusion of moisture from reagents and glassware. Analytical thin layer chromatography (TLC) was performed using EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium molybdate, ethanolic phosphomolybdic acid, or aqueous potassium permanganate. Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on EM Reagents Silica Gel 60 (230-400 mesh). Infrared spectra were recorded on a Perkin Elmer 781 spectrophotometer and are reported in reciprocal centimeters ($cm^{-1}$). Only the most important and relevant frequencies are reported. $^{1}H$ and $^{13}C$ NMR spectra were recorded in deuteriochloroform, unless otherwise noted, on a Varian XL-200, Varian XL-300, Bruker AMX-300, Bruker ARX-400 spectrometer (200.05, 299.95, 300.16, 400.13, MHz respectively). Chemical shifts are reported in ppm on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant in Hz, integration, and assignment. Chemical shifts are reported in ppm from the central peak of deuteriochloroform (76.9 ppm) on the δ scale. Assignments were made from complete proton decoupling and 2D NMR spectra. Optical rotations were determined with a Jasco DIP-360 polarimeter at 589 nm. Data are reported as follows: $[\alpha]_{\lambda}^{temp}$, concentration (*c* g/100mL), and solvent. Combustion analyses were performed by Galbraith Laboratories (Knoxville, TN). High Resolution mass spectra (FAB, CI, EI) were obtained at the Centre Régional de Spectrométrie de Masse of the Université de Montréal. Analytical gas chromatography (GLC) was carried out on a Hewlett Packard 5890 series II gas chromatograph equipped with a split mode capillary injector and a flame ionization detector. Unless otherwise noted, injector and detector temperatures were 250 °C. Data are reported as follows: column type, oven temperature, carrier pressure, and retention time ($t_r$). Analytical High Performance Liquid Chromatography was performed on a Waters 600E Multisolvent delivery System with a U-V/VIS Waters 486 Tunable Absorbance detector. When necessary, solvents and reagents were dried using standard methods. All other reagents were used as received unless stated otherwise.

**3,4,6-Tri-*O*-acetyl-1,2-*O*-(1-ethoxyethylidene)-α-D-glucopyranose (5).** To a solution of glucose pentaacetate (100 g, 0.26 mol) in chloroform (900 mL) at 0 °C was added anhydrous aluminum chloride (41 g, 0.31 mol) in one portion. The suspension was stirred at 0 °C for 4 h, then 2,6-lutidine (250 mL, 2.15 mol) was added over 2 min followed by anhydrous ethanol (700 mL, 11.9 mol). The resulting solution was stirred at room temperature for 24 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (1 L), 2.5 M aq. NaOH (1 L), and $CHCl_3$ (1.5 L). The layers were separated and the aqueous layer was washed twice with $CHCl_3$ (1 L). The combined organic layers were dried over $Na_2SO_4$, and concentrated under reduced pressure. Excess 2,6-lutidine was distilled under vacuum to produce the crude orthoester **5** (64 g, 66%) as a 8:1 mixture of diastereomers that was used directly in the next step without further purification. A small, analytically pure sample could be obtained by recrystallization from ether-hexane to produce orthoester **5** that was identical in all respects to known material:[13] mp 96-97 °C; $[\alpha]_D$ +31° (*c* 1.0, $CHCl_3$); lit.[8] mp 97 °C, $[\alpha]_D$ +31° (*c* 1, $CHCl_3$).

**3,4,6-Tri-*O*-benzyl-1,2-*O*-(1-ethoxyethylidene)-α-D-glucopyranose (6).** To a solution of crude orthoester **5** (*ca.* 0.26 mol) in MeOH (1.5 L) was added a solution of sodium methoxide in methanol (5 mL, 1.1 M, prepared from 2.3 g of sodium and 90 mL of MeOH). The resulting clear solution was stirred at room temperature for 2 h after which time TLC analysis showed complete consumption of starting material and formation of a major product ($R_f$ 0.43 10% MeOH/$CHCl_3$). The orange solution was concentrated under reduced pressure to afford the crude triol as an orange oil that was used directly in the next step without further purification.

A solution of crude triol (*ca.* 0.26 mol) in DMF (1 L) was cooled to 0 °C and sodium hydride (60 g, 1.5 mol, 60% dispersion in oil) was added over 20 min. After 45 min of stirring at 0 °C, a solution of benzyl bromide (152 mL, 1.28 mol) in DMF (100 mL) was added over 1.5 h (exothermic). The ice bath was removed after the addition of *ca.* 125 mL of the benzyl bromide solution. The resulting mixture was stirred at room temperature for 5 h. The reaction mixture was cooled to 0 °C and $H_2O$ (*ca.* 100 mL) was added slowly. The mixture was poured into a separatory funnel containing $H_2O$ (1 L) and ether (3 L). The layers were separated and the organic layer was washed with $H_2O$ (3 x 1 L), saturated aqueous NaCl (1 L), dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to afford a crude orange oil (160 g) that was used directly in the next step without further purification.

A small, analytically pure sample was obtained by flash chromatography using 10% ethyl acetate:hexane as eluent to afford the desired orthoester as a colorless oil that was

identical in all respects to authentic material: $[\alpha]_D$ +34° (*c* 1.0, $CHCl_3$); lit.[9] $[\alpha]_D$ +35° (*c* 1.5, $CHCl_3$).

**3,4,6-Tri-*O*-benzyl-2-*O*-acetyl-α-D-glucopyranose (7).** To a solution of crude orthoester **7** in dichloromethane (2 L) was added HCl washed silica gel (100 g) followed by 10% aqueous HCl (100 mL).[14] The resulting mixture was stirred mechanically for 3 h and then filtered through a fritted disk funnel.[15] The organic solution was diluted to 4 L with $CH_2Cl_2$ and anhydrous potassium carbonate (100 g) was added in one portion. The resulting mixture was stirred mechanically at room temperature for 20 h. The organic layer was filtered through a fritted disk funnel and concentrated under reduced pressure to afford an orange solid. Recrystallization from ether-hexane afforded 55 g (44% overall for 4 steps) of the desired α-lactol as a white solid that was identical to authentic material: mp 126-128 °C (lit.[11] 128-129 °C); $[\alpha]_D$ +54° (*c* 1.0, $CHCl_3$) (lit.[11] $[\alpha]_D$ +55° (*c* 1.1, $CHCl_3$).

**3,4,6-Tri-*O*-benzyl-2-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate (8).** To a solution of lactol **7** (1.50 g, 3.04 mmol) and trichloroacetonitrile (3.1 mL, 30.5 mmol) in anhydrous $CH_2Cl_2$ (12 mL) at -50 °C was added NaH (134 mg, 3.35 mmol, 60% suspension in oil). After 45 min of stirring between -50 °C (bath was allowed to warm to -20 °C over that time), the solution was diluted with ether (150 mL) and $H_2O$ (50 mL). The layers were separated, and the organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography using 16% ethyl acetate-hexane as eluent to produce 1.51 g (78%) of the desired trichloroacetimidate **8** as a colorless oil that was identical in all respects to authentic material: $[\alpha]_D$ +88° (*c* 0.91, $CHCl_3$) (lit.[11] $[\alpha]_{578}$ +81.8° (*c* 1, $CHCl_3$).

**General Procedure for Glycosylation. *Cis*-2'-pentenyl 2-*O*-acetyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (9-OAc).** To a solution of trichloroacetimidate **8** (294.1 mg, 0.462 mmol) in 8.0 mL of $CH_2Cl_2$ (8 mL), was added a solution of *cis*-2-penten-1-ol in $CH_2Cl_2$ (0.9 mL, 0.57 M). The resulting mixture was cooled to -78 °C and a solution of $BF_3 \cdot OEt_2$ in $CH_2Cl_2$ (230 μL, 0.2 M) was added dropwise. The reaction was stirred at -78 °C for 30 min then at to 0 °C for an additional 15 min. The reaction was then quenched with solid $NaHCO_3$, $H_2O$, and diluted with ether. The layers were separated and the aqueous layer was washed twice with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was heated at 60 °C under vacuum (0.1 mmHg) for 9 h to remove the trichloroacetamide by-product. Subsequent flash chromatography on silica gel using 10% to 12% EtOAc/hexanes as eluent, produced the desired 2-*O*-acetyloxy-β-D-glucopyranoside (224 mg, 87%) as a colorless oil (**9-OAc**): $R_f$ 0.18 (10%

EtOAc/hexanes); $[\alpha]_D$ +6.81° (*c* 1.57, $CHCl_3$); IR (KBr) 3080, 3060, 3033, 2960, 2870, 1745, 1250, 1060; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.36-7.16 (m, 15H, $CH_2C_6H_5$), 5.64-5.55 (m, 1H, C*H*=CH), 5.47-5.39 (m, 1H, C*H*=CH), 5.04-4.98 (m, 1H, $H_2$), 4.78 (d, *J* = 11 Hz, 2H, O$CH_2$Ph, O*CH*2Ph), 4.66 (d, *J* = 11 Hz, 1H, O$CH_2$Ph), 4.63 (d, *J* = 12 Hz, 1H, O$CH_2$Ph), 4.55 (d, *J* = 12 Hz, 2H, O$CH_2$Ph, O$CH_2$Ph), 4.40 (d, *J* = 8 Hz, 1H, $H_1$), 4.30 (dd, *J* = 13, 6 Hz, 1H, $CH_2C_4H_7$), 4.23 (dd, *J* = 12, 8 Hz, 1H, $CH_2C_4H_7$), 3.78-3.63 (m, 4H, $H_3$, $H_4$, $H_6$), 3.50-3.44 (m, 1H, $H_5$), 2.09-1.99 (m, 2H, $CH_2CH_3$), 1.96 (s, 3H, OCO*CH*$_3$), 0.94 (t, *J* = 8 Hz, 3H, $CH_2CH_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 169.38, 138.03, 137.98, 137.74, 136.12, 128.28, 128.20, 128.11, 128.06, 127.86, 127.68, 127.56, 127.45, 124.13, 99.12, 82.92, 77.89, 75.02, 74.88, 73.32, 72.93, 68.57, 63.84, 20.80, 20.69, 14.06; HRMS (FAB) calcd for $C_{34}H_{40}O_7$ + $Na^+$ 583.2672. Found 583.2684.

***Cis*-2'-Pentenyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (9).** To a solution of trichloroacetimidate **8** (307.9 mg, 0.483 mmol) in $CH_2Cl_2$ (8.4 mL) was added a solution of *cis*-2-penten-1-ol in $CH_2Cl_2$ (1.0 mL, 0.53 M). The resulting mixture was cooled to -78 °C and a solution of $BF_3$•$OEt_2$ in $CH_2Cl_2$ (240 μL, 0.20 M) was added dropwise. The reaction was stirred at -78 °C for 30 min then at 0 °C for an additional 15 min and a solution of MeONa in MeOH (4.8 mL, 1.0 M) was added in one portion. The bath was removed and the resulting clear solution was stirred 30 min at room temperature. The reaction was then quenched with $H_2O$ and diluted with ether. The layers were separated and the aqueous layer was washed twice with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was heated at 60 °C under vacuum (0.1 mmHg) for 9 h to remove the amide by-product. Subsequent flash chromatography on silica gel using 12% EtOAc/hexanes as eluent produced the desired β-D-glucopyranoside **9** (212 mg, 85%) as a colorless oil: $R_f$ 0.22 (15% EtOAc/hexanes); $[\alpha]_D$ -5.2° (*c* 2.0, $CHCl_3$); IR (Neat) 3480, 3040, 2880, 1460, 1360, 1110, 1065 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.39-7.15 (m, 15H, $C_6H_5$), 5.67-5.48 (m, 2H, C*HCH*$C_2H_5$), 4.94 (d, *J* = 11 Hz, 1H, $CH_2$Ph), 4.84 (d, *J* = 11 Hz, 1H, $CH_2$Ph), 4.83 (d, *J* = 11 Hz, 1H, $CH_2$Ph), 4.62 (d, *J* = 12 Hz, 1H, $CH_2$Ph), 4.54 (d, *J* = 12 Hz, 1H, $CH_2$Ph), 4.53 (d, *J* = 11 Hz, 1H, $CH_2$Ph), 4.38 (dd, *J* = 12, 6 Hz, 1H, $CH_2C_4H_7$), 4.30 (d, *J* = 7 Hz, 1H, $H_1$), 4.26 (dd, *J* = 12, 8 Hz, 1H, $CH_2C_4H_7$), 3.75 (dd, *J* = 11, 2 Hz, 1H, $H_6$), 3.69 (dd, *J* = 11, 4 Hz, 1H, $H_6$), 3.62-3.55 (m, 3H, $H_2$, $H_3$, $H_4$), 3.50-3.44 (m, 1H, $H_5$), 2.42 (bs, 1H, OH), 2.12-2.05 (m, 2H, $CH_2CH_3$), 0.96 (t, *J* = 8 Hz, 3H, $CH_2CH_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 138.5, 138.0, 137.9, 136.4, 128.3, 128.2, 128.2, 127.9, 127.8, 127.8, 127.6, 127.5, 127.4, 124.0, 101.1, 84.4, 75.0, 75.0, 74.8, 74.5, 73.3, 68.7, 64.3, 20.7, 14.1; HRMS (FAB) calcd for $C_{32}H_{33}O_6$-H 517.2590. Found 517.2599 (M-H).

***Trans*-3'-Methyl-2'-butenyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (10).** The β-glucopyranoside **10** was prepared as described for compound **9** and isolated in 84% yield as a white solid: mp 55-56.5 °C; $R_f$ 0.35 (20% EtOAc/hexanes); $[\alpha]_D$ -11.2° (*c* 1.1, $CHCl_3$); IR (KBr) 3380 (br), 2900, 2880, 1600, 1490, 1450 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.4-7.17 (m, 15H, $C_6H_5$), 5.41-5.36 (m, 1H, $CH$=$C(CH_3)_2$), 4.95 (d, *J* = 11 Hz, 1H, $CH_2Ph$), 4.85 (d, *J* = 11 Hz, 1H, $CH_2Ph$), 4.84 (d, *J* = 11 Hz, 1H, $CH_2Ph$), 4.63 (d, *J* = 12 Hz, 1H, $CH_2Ph$), 4.55 (d, *J* = 12 Hz, 1H, $CH_2Ph$), 4.54 (d, *J* = 11 Hz, 1H, $CH_2Ph$), 4.36 (dd, *J* = 12, 7 Hz, 1H, $OCH_2C_4H_7$), 4.30 (d, *J* = 7 Hz, 1H, $H_1$), 4.20 (dd, *J* = 12, 8 Hz, 1H, $OCH_2C_4H_7$), 3.76 (dd, *J* = 11, 2 Hz, 1H, $H_6$), 3.71 (dd, *J* = 11, 5 Hz, 1H, $H_6$), 3.65-3.55 (m, 3H, $H_2$, $H_3$, $H_4$), 3.53-3.47 (m, 1H, $H_5$), 2.37 (bs, 1H, CHO*H*), 1.77 (s, 3H, $CH_3$), 1.70 (s, 3H, $CH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 138.7, 138.2, 138.1, 128.3, 128.2, 128.2, 127.8, 127.6, 127.5, 127.5, 127.4, 120.0, 101.2, 84.6, 77.7, 75.3, 74.9, 74.8, 74.7, 73.4, 69.1, 65.4, 25.6, 17.9; HRMS (FAB) calcd for $C_{32}H_{38}O_6$+H 519.2746. Found 519.2708 (M+H).

***Trans*-3'-Phenyl-2'-propenyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside (11).** The β-glucopyranoside **11** was prepared as described for compound **9** and isolated in 87% yield as a white solid: mp 83-84.5 °C; $R_f$ 0.27 (20% EtOAc/hexanes); $[\alpha]_D$ -14.36° (*c* 1.1, $CHCl_3$); IR (KBr) 3490 (br), 3020, 2880, 1450, 1360; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.39-7.17 (m, 20H, $C_6H_5$), 6.64 (d, *J* = 16 Hz, 1H, CH=C*H*Ph), 6.36-6.28 (m, 1H, C*H*=CHPh), 4.92 (d, *J* = 11 Hz, 1H, $CH_2Ph$), 4.85 (d, *J* = 11 Hz, 1H, $CH_2Ph$), 4.84 (d, *J* = 11 Hz, 1H, $CH_2Ph$), 4.64 (d, *J* = 11 Hz, 1H, $CH_2Ph$), 4.59-4.53 (m, 3 H, $OCH_2C_2H_2Ph$, $CH_2Ph$), 4.38 (d, *J* = 8 Hz, 1H, $H_1$), 4.30 (dd, *J* = 13, 7 Hz, 1H, $H_5$), 3.76 (dd, *J* = 11, 2 Hz, 1H, $H_6$), 3.71 (dd, *J* = 11, 5 Hz, 1H, $H_6$), 3.66-3.58 (m, 3H, $H_2$, $H_3$, $H_4$), 3.52-3.48 (m, 1H, $H_5$), 2.36 (bs, 1H, CHO*H*); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 138.8, 138.4, 136.7, 133.2, 128.5, 128.3, 128.2, 128.1, 127.8, 127.8, 127.7, 127.6, 127.5, 127.5, 126.5, 125.2, 101.9, 84.7, 77.9, 75.5, 75.0, 74.8, 73.6, 69.8, 69.4; HRMS (FAB) calcd for $C_{36}H_{38}O_6$+H 567.2746. Found 567.2753.

***Cis*-2'-Pentenyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (12).** To a solution of trichloroacetimidate **8** (827 mg, 1.30 mmol) and *cis*-2-penten-1-ol (197 μL, 1.95 mmol) in anhydrous $CH_2Cl_2$ (26 mL) at -78 °C was added $BF_3$•$OEt_2$ (160 μL, 1.30 mmol) over 15 min. The resulting heterogeneous solution was stirred at that temperature for 10 min and then at 0 °C for an additional 10 min. The reaction mixture was recooled to -78 °C and freshly distilled $TiCl_4$ (143 μL, 1.30 mmol) was added over 30 sec. After the addition, the yellow mixture was stirred at -78 °C for 15 min and then at 0 °C for 1 h. The cleavage of the 2-*O*-acetyl group was accomplished by the addition of triethylamine (902 μL, 6.49 mmol) and sodium methoxide in methanol (7.4 mL, 1.75 M). After being

stirred for 15 min at room temperature, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ether (120 mL) and the organic layer was washed with 5% aq. HCl, $H_2O$, 1 M NaOH, and sat. aq. NaCl. The organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The by-product trichloroacetamide was removed by sublimation under vacuum (40-50 °C, 0.1 mmHg). Flash chromatography of the residue using 5% ethyl acetate:chloroform as eluent afforded the desired glucopyranoside (626 mg, 93%) as a white solid: mp 79-82 °C (ether:hexane); $R_f$ 0.44 (30% ethyl acetate:hexane); $[\alpha]_D$ +106.9° (*c* 0.9; $CHCl_3$); IR (KBr) 3460, 2910, 1450, 1160, 740, 690 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.40-7.14 (m, 15H, $C_6H_5$), 5.70-5.40 (m, 2H, $CHCHC_2H_5$), 4.95 (d, *J* = 11 Hz, 1H, $OCH_2Ph$), 4.94 (d, *J* = 4 Hz, 1H, $H_1$), 4.84 (d, *J* = 11 Hz, 1H, $OCH_2Ph$), 4.83 (d, *J* = 11 Hz, 1H, $OCH_2Ph$), 4.64 (d, *J* = 12 Hz, 1H, $OCH_2Ph$), 4.52 (d, *J* = 12 Hz, 1H, $OCH_2Ph$), 4.51 (d, *J* = 11 Hz, 1H, $OCH_2Ph$), 4.24 (dd, *J* = 12, 6 Hz, $CH_2C_4H_7$), 4.13 (dd, *J* = 12, 7 Hz, $OCH_2C_4H_7$), 3.81-3.63 (m, 6H, $H_2$, $H_3$, $H_4$, $H_5$), 2.08 (m, 3H, CHO*H*, $CH_2CH_3$), 0.98 (t, *J* = 7.5 Hz, 3H, $CH_2CH_3$); $^{13}C$ NMR (50.3 MHz, $CDCl_3$) δ 138.7, 138.2, 138.0, 136.3, 128.3, 127.8, 127.7, 124.1, 97.5, 83.5, 77.4, 75.3, 75.0, 73.5, 73.0, 70.6, 68.5, 63.0, 20.8, 14.2.

Anal. Calcd for $C_{32}H_{38}O_6$: C, 74.11; H, 7.38. Found: C, 73.84; H, 7.52.

***Trans*-2'-Hexenyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (13).** The α-glucopyranoside **13** was prepared as described for compound **12** and isolated in 81% yield as a colorless oil: $[\alpha]_D$ +22.4° (*c* 1.40, $CHCl_3$); IR (NaCl) 3480, 2920, 2860, 1500, 1450, 1350, 740, 690 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.39-7.12 (m, 15H, $C_6H_5$), 5.70 (m, 1H, $OCH=CHC_3H_7$), 5.54 (m, 1H, $OCH=CHC_3H_7$), 4.95 (d, *J* = 11 Hz, 1H, $CH_2Ph$), 4.94 (d, *J* = 3 Hz, 1H, $H_1$), 4.84 (d, *J* = 11 Hz, 1H, $CH_2Ph$), 4.83 (d, *J* = 11 Hz, 1H, $CH_2Ph$), 4.64 (d, *J* = 12 Hz, 1H, $CH_2Ph$), 4.50 (d, *J* = 12 Hz, 1H, $CH_2Ph$), 4.48 (d, *J* = 11 Hz, 1H, $CH_2Ph$), 4.16 (dd, *J* = 12 Hz et 6 Hz, 1H, $OCH_2C_5H_9$), 3.97 (dd, *J* = 12 Hz et 7 Hz, 1H, $OCH_2C_5H_9$), 3.84-3.59 (m, 6H, $H_2$, $H_3$, $H_4$, $H_5$, $H_6$), 2.11 (d, *J* = 8 Hz, 1H, CHO*H*), 2.01 (q, *J* = 7 Hz, 2H, $CH_2C_2H_5$), 1.40 (m, *J* = 7 Hz, 2H, $CH_2CH_3$), 0.90 (t, *J* = 7 Hz, 3H, $CH_2CH_3$); $^{13}C$ NMR (50.3 MHz, $CDCl_3$) δ 138.7, 138.2, 137.9, 135.7, 128.3, 127.9, 127.7, 127.6, 125.2, 97.2, 83.5, 77.4, 75.3, 75.0, 73.5, 73.0, 70.5, 68.5, 68.3, 34.3, 22.1, 13.7. HRMS (FAB) calcd for $C_{33}H_{40}O_6$-H 531.2747. Found: 531.2762.

**3'-Methyl-2'-butenyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (14).** The α-glucopyranoside **14** was prepared as described for compound **12** and isolated in 9% yield as a colorless oil (a 47% yield was obtained if the anomerization was carried out on the pure, isolated acetate): $[\alpha]_D$ 98.1° (*c* 0.83, $CHCl_3$); IR (NaCl) 3500, 2900, 1495, 1450, 1360, 1060, 730, 690 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7,39-7,12 (m, 15H, $C_6H_5$), 5,33 (t, *J* = 7 Hz, 1H, $CH=C(CH_3)_2$), 4,97-4,90 (m, 2H, $H_1$, $OCH_2Ph$), 4,83 (d, *J* = 11

Hz, 2H, OC$H_2$Ph), 4,63 (d, $J$ = 12 Hz, 1H, OC$H_2$Ph), 4,50 (m, 2H, OC$H_2$Ph), 4,23 (dd, $J$ = 12 Hz et 7 Hz, 1H, C$H_2C_4H_7$), 4,09 (dd, $J$ = 12 Hz et 8 Hz, 1H, OC$H_2C_4H_7$), 3,85-3,57 (m, 6H, $H_2$, $H_3$, $H_4$, $H_5$, $H_6$), 2,17 (d, $J$ = 8 Hz, 1H, CHO$H$), 1,73 (s, 3H, C$H_3$), 1,67 (s, 3H, C$H_3$) ppm; $^{13}$C NMR (50.3 MHz, $CDCl_3$) δ 138.7, 138.1, 137.9, 137.8, 128.3, 127.8, 127.6, 127.5, 119.9, 97.2, 83.5, 77.4, 75.2, 74.9, 73.4, 73.0, 70.4, 68.5, 63.9, 25.7, 17.9.

**Propyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (16).** The α-glucopyranoside **16** was prepared as described for compound **12** and isolated in 86% yield as a white solid: mp 45-48 °C; $R_f$ 0.24 (20% ethyl acetate-hexane); $[\alpha]_D$ +89.1° (*c* 1.03, $CHCl_3$); IR (KBr) 3450, 2920, 1450, 1130, 1060, 720, 690 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.41-7.14 (m, 15H, $C_6H_5$), 4.96 (d, $J$ = 11 Hz, 1H, OC$H_2$Ph), 4.89 (d, $J$ = 3 Hz, 1H, C$H$OC$_4$H$_9$), 4.84 (d, $J$ = 11 Hz, 1H, OC$H_2$Ph), 4.83 (d, $J$ = 11 Hz, 1H, OC$H_2$Ph), 4.64 (d, $J$ = 12 Hz, 1H, OC$H_2$Ph), 4.51 (d, $J$ = 12 Hz, 1H, OC$H_2$Ph), 4.50 (d, $J$ = 11 Hz, 1 H, OC$H_2$Ph), 3.78-3.65 (m, 6H, $H_2$, $H_3$, $H_4$, $H_5$, $H_6$), 3.47 (dt, $J$ = 10, 8 Hz, 2H, OC$H_2$Pr), 2.05 (bs, 1H, CHO$H$), 1.70-1.57 (m, 2H, C$H_2$Et), 1.45-1.30 (m, 2H, C$H_2$Me), 0.93 (t, $J$ = 7 Hz, 3H, C$H_3$); $^{13}$C NMR (50.3 MHz, $CDCl_3$) δ 138.7, 138.1, 137.9, 128.3, 128.3, 127.96, 127.90, 127.89, 127.87, 127.82, 127.79, 127.77, 127.67, 127.63, 127.56, 98.3, 83.6, 77.4, 75.3, 75.0, 73.5, 73.0, 70.5, 68.5, 67.9, 31.5, 19.3, 13.8; HRMS (FAB) Calcd for $C_{31}H_{38}O_6$: 505.2590. Found: 505.2599.

**5'α-Androstan-3'α-yl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (17).** The α-glucopyranoside **17** was prepared as described for compound **12** and isolated in 58% yield as a white solid: mp 85-87 °C; $R_f$ 0.48 (25% ethyl acetate-hexane); $[\alpha]_D$ +91.8° (*c* 1.00, $CHCl_3$); IR (KBr) 3500, 2920, 1580, 1450, 1050, 1020, 730, 690 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.42-7.25 (m, 15H, $C_6H_5$), 5.03 (d, $J$ = 3 Hz, 1H, $H_1$), 4.98 (d, $J$ = 11 Hz, 1H, OC$H_2$Ph), 4.83 (d, $J$ = 11 Hz, 1H, OC$H_2$Ph), 4.64 (d, $J$ = 12 Hz, 1H, OC$H_2$Ph), 4.50 (d, $J$ = 12 Hz, 1H, OC$H_2$Ph), 4.48 (d, $J$ = 11 Hz, 1H, OC$H_2$Ph), 3.91-3.55 (m, 7H, $H_2$, $H_3$, $H_4$, $H_5$, $H_6$), 2.06 (d, $J$ = 9 Hz, 1H, CHO$H$), 1.85-0.64 (m, 24H, OCHC$_{16}H_{24}$), 0.80 (s, 3H, C$H_3$), 0.69 (s, 3H, C$H_3$); $^{13}$C (75 MHz, $CDCl_3$) δ 138.7, 138.1, 137.8, 128.2, 127.8, 127.7, 127.5, 127.4, 96.8, 83.6, 77.33, 77.26, 75.2, 74.9, 73.3, 72.8, 70.3, 68.5, 54.40, 54.35, 44.8, 40.7, 40.3, 38.7, 36.7, 35.9, 35.7, 35.5, 32.3, 28.6, 27.7, 25.4, 21.1, 20.4, 17.4, 12.2; HRMS (FAB) Calcd for $C_{46}H_{60}O_6$: 731.4288 ($M^+$+Na). Found: 731.4333.

## ACKNOWLEDGMENT

This research was supported by the NSERC of Canada, Bio-Méga Inc., the F.C.A.R. (Québec) and the Université de Montréal. B. C. thanks the F.C.A.R. (Québec) for a post-graduate fellowship. We also thank Prof. S. Hanessian for helpful suggestions.

## REFERENCES AND NOTES


1. NSERC (Canada) University Research Fellow, 1989-1994; Bio-Méga Young Investigator, 1991-1993.
2. A. B. Charette, B. Côté, and J.-F. Marcoux, *J. Am. Chem. Soc.*, **113**, 8166 (1991).
3. A. B. Charette, N. Turcotte, and J.-F. Marcoux, Submitted for publication.
4. For a review on anomerization of glycosides see: E. Pacsu, J. Janson, and B. Lindberg in *Methods in Carbohydr. Chem.*, Vol. II; R. L. Whistler and M. L. Wolfrom, Eds; Academic Press: New York, 1963, p 377.
5. a) S. Koto, N. Morishima, R. Kawahara, K. Ishikawa, and S. Zen, *Bull. Chem. Soc. Jpn.*, **55**, 1092 (1982).
   b) N. Morishima, S. Koto, and S. Zen, *Chem. Lett.*, 749 (1979).
6. N. Ikemoto, O.-K. Kim, L.-C. Lo, V. Satyanarayana, M. Chang, and K. Nakanishi, *Tetrahedron Lett.*, **33**, 4295 (1992).
7. R. R. Schmidt and J. Michel, *Angew. Chem. Int. Ed. Engl.*, **19**, 731 (1980).
8. a) R. U. Lemieux and J. D. T. Cipera, *Can. J. Chem.*, **34**, 906 (1956).
   b) N. K. Kochetkov, A. J. Khorlin, and A. F. Bochkov, *Tetrahedron*, **23**, 693 (1967).
9. M. A. E. Shaban and R. W. Jeanloz, *Carbohydr. Res.*, **52**, 103 (1976) and references cited therein.
10. Lactol **1** can be precipitated selectively upon addition of 20% ether-hexane.
11. a) R. R. Schmidt and G. Effenberger, *Liebigs Ann. Chem.*, 825 (1987).
    b) R. R. Schmidt and G. Effenberger, *Carbohydr. Res.*, **171**, 59 (1987).
12. It was found that the addition of 1 equivalent of $TiCl_4$ was not sufficient to anomerize the β-glycoside if a catalytic amount (0.1 eq) of $BF_3{\cdot}OEt_2$ was used.
13. The use of "Identical in all respects to known material" throughout the paper implies that physical data ($^1H$, $^{13}C$ NMR, and IR) of the synthetic compound were identical to literature data.
14. An additional 100 mL of 10% aq. HCl is sometimes required depending on the amount of residual 2,6-lutidine left in the crude mixture.
15. Concentration of the organic solution provided a chromatographically unseparable 2:1 mixture of **7**:**1**.