

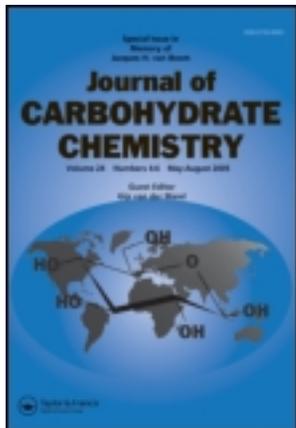
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Application of Ball Milling Technology to Carbohydrate Reactions: I. Regioselective Primary Hydroxyl Protection of Hexosides and Nucleoside by Planetary Ball Milling[‡]

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National Institute of Pharmaceutical Education and Research, Department of Medicinal Chemistry, Punjab, India

Dry ball milling of hexosides with trityl chloride in the presence of DABCO or Na₂CO₃ has been found to result in their complete conversion to the respective 6-*O*-trityl ethers. Further wet grinding of the reaction mixture with Ac₂O in the presence of DMAP led to the respective fully protected hexosides in good to excellent yields after isolation. It has been found to be an effective one-pot two-step synthesis under solvent-free condition. The speed of homogenization has been shown to highly influence the rate and outcome of the reaction, and commercially available planetary ball mill has been proved to be very convenient for carrying out the reaction under standardized and reproducible conditions.

Keywords Trityl ethers, Regioselective reactions, Ball mill, Solvent-free synthesis, Mechanochemical reactions

INTRODUCTION

Complexity in the structures of biologically important carbohydrates and their derivatives makes their synthesis a challenging and difficult task that involves

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multi-step processes requiring selective functional group manipulations. Selective protection of the primary hydroxyl group in hexosides and nucleosides by bulky acid-labile groups such as trityl (Tr), *t*-butyldimethylsilyl (TBDMS), *t*-butyldiphenylsilyl (TBDPS), etc., is very widely applied in synthetic oligosaccharide and nucleoside chemistry.^[1] The classical approach for this reaction involves treatment of the respective glycoside or nucleoside with the desired organic halide in pyridine, which serves both as the solvent and catalyst for the reaction.^[1,2] Alternatively, use of dimethylaminopyridine (DMAP) either alone or in combination with Et₃N,^[3] imidazole,^[4] 2,4,6-collidine,^[5] DBU,^[6] 2,6-lutidine,^[7] etc., as catalyst in a suitable solvent such as DMF,^[3–5] DCM,^[6–7] or MeCN^[8] is also recommended. Some of these instances involve use of some of the more expensive reagents such as TBDMS triflate^[7] and *N*-trityl pyridiniumfluoroborate^[8] as the respective donor reagents. In addition, solid phase tritylation^[5] and tritylation in molten salts,^[9] as well as one involving the use of the TMS derivative of both the alcohol to be silylated and trityl alcohol in the presence of TMSOTf,^[10] have also been reported. Thus, the *O*-tritylation reactions most often require environmentally unfriendly solvents such as pyridine and DMF or expensive catalysts/reagents such as DMAP, trityl triflate, *N*-trityl pyridiniumfluoroborate, etc. Hence, solvent-free synthesis proves more environmentally benign and economically feasible and is extremely important in the context of the fact that waste minimization has become an essential part of the regulatory issues associated with the chemical industry worldwide. In this context, ball milling, a mechanochemical technology scarcely used in synthetic organic chemistry, seemed particularly attractive.^[11] In this report we describe results of our recent work on the regioselective etherification of hexosides and nucleoside by planetary ball milling. (In planetary ball milling the grinding jar rotates about its own axis as well as around the common axis of the sun wheel in the opposite direction. This results in high pulverization energy and efficient mixing.)

RESULTS AND DISCUSSION

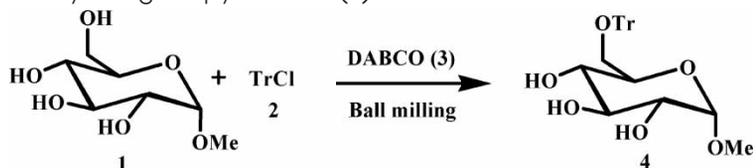
For the synthesis of the α - and β -(1,6)-linked *galacto*- and *gluco*-oligosaccharides in progress in our laboratory, multigram quantities of the corresponding chemoselectively protected monosaccharide building blocks **15a–15c**, **17**, **19**, **21**, and **23**, obtainable from **1**, **16**, **18**, **20**, and **22**, respectively via, the corresponding 6-*O*-substituted ethers, were required. Toward this end and with a view to reducing the use of harmful and high-boiling liquids such as pyridine and DMF, the reaction of methyl α -D-glucopyranoside (**1**) with trityl chloride (**2**) under solvent-free conditions was investigated. For the reaction conditions to be reproducible, use of a commercially available ball mill was considered desirable instead of the grinding/mixing carried out manually using a mortar and pestle. A planetary ball mill wherein the conditions of grinding/mixing can be electronically controlled/preset as desired seemed to be able to

serve the purpose. Indeed, when a mixture of the glucoside (**1**, 1 mmol), trityl chloride (**2**, 1.25 mmol), and DABCO (**3**, 1.25 mmol) was allowed to mix at 500 rpm overnight chromatographically, pure 6-*O*-trityl derivative **4**^[12] was obtained as crystalline solid in 67% of isolated yield (Sch. 1). It was identical with authentic **4** prepared by a literature procedure,^[3a] and was further characterized as its triacetate **15a**.^[13]

Optimization of the reaction condition with respect to the concentration of **2** and **3** (with **2:3** at 0.5:1, 1:1, 1.25:1.25, 2.5:1.25, 1.25:2.5, 2.5:2.5, and 3.75:2.5 mol ratio, respectively, per mol of the glucoside **1** at 500 rpm for 15 h) was then carried out and the best results were obtained when 2.5 mol each of **2** and **3** per mol of compound **1** were used for the reaction. Under these conditions complete consumption of **1** was indicated by TLC (eluent, CH₂Cl₂:MeOH, 8:2) and isolation of the product by column chromatography (silica gel; eluent, EtOAc:*n*-Hex, 4:1) afforded the desired crystalline 6-*O*-trityl ether **4** in 80% yield. Alternatively, as it had been possible in most of the cases studied, the product could also be obtained from the crude mixture directly by crystallization. Choice of organic solvents was limited in the case of unprotected carbohydrates and nucleosides because of solubility difficulties and avoidance of organic solvents as an aim of current regulatory concern and compliance. The reaction described above constitutes the first example of the application of solvent-free regioselective tritylation in synthetic carbohydrate chemistry. Application of DABCO, a relatively cheap base, as a catalyst for the reaction described above is also new.

As the speed of milling was expected to influence the dynamic impact energy produced during the process, the effect of this variable on the outcome of the reaction was studied. Thus, in separate experiments compounds **1**, **2**, and **3** (mol ratio, 1:2.5:2.5, respectively) were homogenized in the mill at different speeds (Table 1) and the yield of the purified product obtained was estimated. Indeed, the speed of operation was found to have a direct bearing on the rate of the reaction and the product yield, both being increased with increasing speed. Thus, while at 100 rpm no product formation was observed for a period of 24 h, significant yields were obtained by increasing it to 400 rpm for 15 to 24 h, and at a setting of 600 rpm complete disappearance of the starting material was observed in only 3 h. The effect of speed of milling on the reaction time and the product yield is clearly evident from Table 1.

It was observed that the reactions at 500 rpm and above resulted in the formation of an intermediate molten mass (visible on observation of the reaction mixture before completion of the reaction), which eventually turned into solids on completion of the reaction. Similar observations in other solid/solid organic reactions have been reported previously.^[14] Other organic/inorganic bases as possible alternatives to DABCO for the reaction were then investigated and the results are summarized in Table 2.

Table 1: Effect of milling speed on the regioselective tritylation of methyl α -D-glucopyranoside (**1**).^a

Scheme 1

Entry	rpm	Time (h)	Isolated yield (%)
1	100	24	0
2	200	24	21
3	300	15	32
4	300	24	39
5	400	15	55
6	400	24	58
7	500	15	80
8	600	3 (15) ^b	87

^aThe reaction was carried out with 1 mmol of the glucoside **1** at **1:2:3** in the ratio 1:2.5:2.5.

^bThe reaction was complete in 3 h but the product was isolated after 15 h in the mill.

Table 2: Effect of base on the regioselective tritylation of **1**.^a

Entry	Base	Time (h)	Isolated yield ^d (%)
1	None	24	0
2	NaOH	15	0
3	KOH	15	25
4	Na ₂ CO ₃	15	71
5 ^b	Na ₂ CO ₃	6	92
6 ^c	Na ₂ CO ₃	2	93
7	K ₂ CO ₃	15	64
8	Cs ₂ CO ₃	15	35
9	Ag ₂ CO ₃	15	73
10	DMAP	24	0
11	Imidazole	15	62

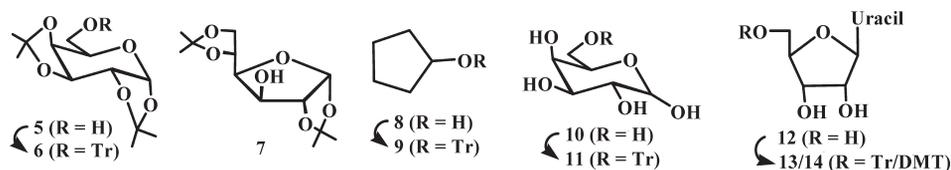
^aReactions were carried out with 1 mmol of the glucoside **1** at 1:2:Base in the ratio 1:2.5:2.5 at 500 rpm.

^bReaction was carried out with 15 g (77.2 mmol) of the glucoside **1** at 1:2:Base in the ratio 1:2.5:2.5 at 500 rpm.

^cReaction was carried out with 15 g (77.2 mmol) of the glucoside **1** at 1:2:Base in the ratio 1:2.5:2.5 at 600 rpm.

^dThe remaining was the unreacted starting material except in entries 5 and 6 where no starting material was detected.

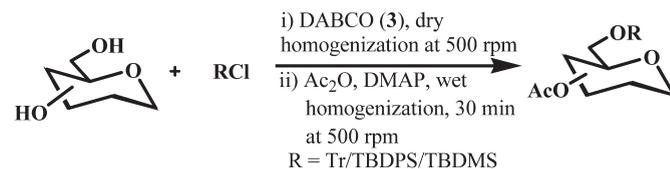
Thus, among the common inorganic bases studied, anhydrous Na_2CO_3 and Ag_2CO_3 were found to be effective for the reaction (Table 2, entries 4 and 8, respectively), although they were not as efficient as DABCO. While the inefficiency of strongly basic alkali metal hydroxides for the reaction (entries 2 and 3, Table 2) could presumably be attributed to the strong nucleophilic character of the hydroxide ion, leading to the hydrolysis of the halide reagent **2**, the failure with DMAP was somewhat surprising yet reasonable as seen by the possibility for the formation of a stable pyridinium salt by reaction with **2**. Indeed, when a mixture of DMAP and **2** was ground under solvent-free conditions in the ball mill (2 h, 500 rpm), the respective pyridinium salt was obtained in quantitative yield.^[15] Another interesting feature of this reaction noticed was that the reactions were significantly more efficient, both in terms of the yield and the reaction time, when carried out in multigram quantities of the substrate. Thus, the 6-*O*-tritylation of **1** in the presence of Na_2CO_3 when carried out at a 15 g scale went to completion in 6 h at 500 rpm and in 2 h at 600 rpm (entries 5 and 6, respectively, Table 2). Further, as evident from these experiments (entries 5 and 6, Table 2), in large-scale preparations Na_2CO_3 , a greener (as well as cheaper) substitute for DABCO, was consistently seen to be as efficient as DABCO.



Among the other substrates subjected to the tritylation reaction in the mill were the partially protected diacetone derivatives **5** and **7**, a native hexose **10**, and the nucleoside **12**. Compound **5**, although bearing a primary hydroxyl group, but being sticky in nature in the mill, gave the tritylated product **6**^[16] in only 59% yield (5 h, 500 rpm). As was to be expected, the acetone **7** bearing a relatively hindered secondary hydroxyl group on *C*-3 was virtually unreactive to tritylation in the ball mill. In sharp contrast, cyclopentanol (**8**) yielded the expected trityl ether **9**^[17] in 96% isolated yield in 5 h at 500 rpm. Further, while *D*-galactose (**10**) did not give any appreciable yield of the desired 6-*O*-trityl derivative (**11**) at 500 rpm for 24 h, the reaction proceeded well at 600 rpm and the regioselectively substituted 6-*O*-trityl-*D*-galactose (**11**,^[18] characterized unambiguously as its corresponding anomeric tetra-*O*-acetates by NMR) was obtained in reasonable yield (47%) in 15 h. Likewise, uridine (**12**) was converted to its 5'-*O*-trityl derivative **13**^[9,19] and 5'-*O*-dimethoxytrityl derivative **14**,^[20] both highly valuable building blocks in nucleotide synthesis, in 43% and 44% yield, respectively, by grinding it with **2**/DMTCl (2.5 mol equiv), respectively, in the presence of DABCO (2.5 mol equiv) for 15 h at 600 rpm without having to use any

solvent or phase transfer catalyst.^[9] It may be recalled that similar reactions under microwave irradiation were also characterized by low yields as well as undesired depurination.^[9] Also, these reactions in ionic liquids, in spite of their relatively high solubilizing power toward the nucleoside, have been reported to proceed over long reaction times with low yields of the desired 5'-*O*-DMT derivative.^[9]

As the overall objective was to obtain chemoselectively protected monosaccharide building blocks, conversion of the trityl ether **4** to its tri-*O*-acetate **15a** in the same pot was highly desirable. Hence, upon completion of the tritylation reaction as described above, DMAP (1 mol equiv) and Ac₂O (1.5 mol equiv per OH group) were added to the reaction mixture, which was wet-milled for 30 min at 500 rpm, whereby complete transformation of **4** into a faster-moving compound with R_f = 0.41 (TLC, eluent, EtOAc:*n*-Hex, 1:3; compound **4** was immobile in this eluent system) took place, which upon aqueous workup and chromatography (silica gel, eluent, EtOAc:*n*-Hex, 1:9) yielded (71%) a crystalline compound identical to authentic **15a** (entry 1, Table 3). In spite of the presence of DABCO in the reaction mixture, the acetylation did not go to completion without the added DMAP. It is also to be noted that if the fully protected derivatives such as **15a** are the desired compound (by successive one-pot tritylation followed by acetylation), the use of Na₂CO₃ in the tritylation step is not recommended because of the possible formation of CO₂ in the acetylation step. The reaction was then successfully scaled up to 5 g without affecting the yield. Encouraged by these results, the reaction of **1** with TBDPSCl (a liquid at rt) and TBDMSCl (a sticky solid at rt) in the presence of DABCO was investigated. The expected products in these reactions were compounds **15b** and **15c** after the *O*-acetylation of the respective initially formed 6-*O*-substituted product. Thus, as noted before, while the reaction of **1** with TrCl (**2**) took 15 h for completion at 500 rpm, that with TBDPSCl was complete in 6 h and **15b**^[17] was isolated in 72% yield after the subsequent one-pot acetylation. The reaction with TBDMSCl was, however, not complete in 15 h at 500 rpm (increasing the milling speed to 600 rpm also did not enable completion of this reaction) and the yield of the respective acetylated product **15c**^[18] obtained was only 49% (82% based on the isolated methyl tetra-*O*-acetyl- α -D-glucopyranoside derived from the unreacted **1**). The inefficiency observed in the reaction of **1** with TBDMSCl could be attributed to the formation of a highly sticky mass in the ball mill, which indeed prevented the mixture from getting mixed effectively. It may be pointed out that in the latter case the balls used in the mill were found to be glued to each other and to the wall, making their effective movement virtually impossible (unlike in the other two cases). Incorporation of molecular sieves (powder, 4Å) resulted in a marginally improved isolated yield of **15c** (being increased to 55% only). The procedure was then successfully extended to other *gluco*- and *galacto*-configured monosaccharide glycosides to obtain the corresponding *O*-acetylated 6-*O*-trityl ethers **17**, **19**, **21**, and **23** from **16**, **18**, **20**, and **22**, respectively (entries 4–7, Table 3).

Table 3: One-pot two-step synthesis of variously protected carbohydrates by ball milling.^a

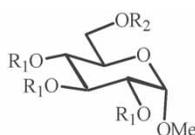
Sr. no.	Substrate sugar	Product after steps i & ii	Time (step i, h)	Yield (%)
1 ^b	Methyl glucoside 1	Tri- <i>O</i> -acetyl-6- <i>O</i> -trityl glucoside 15a (13)	15	71
2	Methyl glucoside 1	Tri- <i>O</i> -acetyl-6- <i>O</i> - ^t butyldiphenylsilyl glucoside 15b (21)	6	72
3	Methyl glucoside 1	Tri- <i>O</i> -acetyl-6- <i>O</i> - ^t butyldimethylsilyl glucoside 15c (22)	15	49 (82) ^c
4	Methyl galactoside 16	Tri- <i>O</i> -acetyl-6- <i>O</i> - trityl galactoside 17 (23)	15	80
5	2-(Trimethylsilyl)ethyl galactoside 18	Tri- <i>O</i> -acetyl-6- <i>O</i> -trityl galactoside 19	15	85
6	Phenyl 1-thio-galactoside 20	Tri- <i>O</i> -acetyl-6- <i>O</i> -trityl 1-thio-galactoside 21	15	82
7	Methyl 1-thio-glucoside 22	Di- <i>O</i> -acetyl-6- <i>O</i> -trityl 1-thio-glucoside 23	15	39 (91) ^c

^aReactions were carried out with substrate (1 mmol):RCl:3 in the ratio 1:2.5:2.5 for (i) and substrate:DMAP:Ac₂O in the ratio 1:1:1.5 per-OH group for (ii).

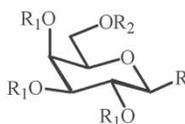
^bThe reaction was scaled up to 5-g scale without affecting the yield.

^cYield based on the recovered starting material in the *O*-acetylated form.

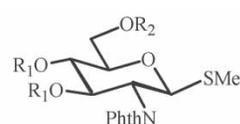
The glucosamine derivative **22**, in which a highly sticky mass was found to be formed during the milling, again, gave poor yield of the product **23** (only 39%, entry 7, Table 3).



15a $R_1 = \text{Ac}, R_2 = \text{Tr}$
15b $R_1 = \text{Ac}, R_2 = \text{TBDPS}$
15c $R_1 = \text{Ac}, R_2 = \text{TBDMS}$



16 $R = \text{OMe}, R_1 = R_2 = \text{H}$
17 $R = \text{OMe}, R_1 = \text{Ac}, R_2 = \text{Tr}$
18 $R = \text{OCH}_2\text{CH}_2\text{SiMe}_3, R_1 = \text{H}, R_2 = \text{Tr}$
19 $R = \text{OCH}_2\text{CH}_2\text{SiMe}_3, R_1 = \text{Ac}, R_2 = \text{Tr}$
20 $R = \text{SPh}, R_1 = \text{Ac}, R_2 = \text{Tr}$
21 $R = \text{SPh}, R_1 = \text{Ac}, R_2 = \text{Tr}$



22 $R_1 = R_2 = \text{H}$
23 $R_1 = \text{H}, R_2 = \text{Tr}$

CONCLUSION

A commercially available planetary ball mill was successfully used for the regioselective 6-*O*-tritylation/silylation of various monosaccharides or their derivatives under solvent-free conditions by dry grinding. The reactions could be carried out on preparative scale with high efficiency in the presence of Na_2CO_3 as catalyst. Successive acetylation by wet grinding was found to be an efficient one-pot two-step protocol for the preparation of the corresponding fully protected carbohydrate derivatives useful in the synthesis of building blocks for oligosaccharide synthesis. As standardized and reproducible conditions for homogenizations have been made possible by the choice of commercially available equipment, clear observations on the effect of speed and duration of homogenization on the rate and the yield of the reaction have been made possible in the present study. Ball milling technology when applied to reactions such as those reported here can lead to significant reduction in the use of hazardous solvents such as pyridine and DMF. Application of ball milling technology to other carbohydrate reactions is currently under way in our laboratory.

EXPERIMENTAL

Melting points were recorded on Mettler DSC 851 or capillary melting point apparatus and are uncorrected. Specific rotations were obtained on AUTOPOL IV polarimeter at 20°C. IR spectra were recorded on Nicolet FT-IR Impact 410 instrument either as neat or KBr pellets. NMR spectra were recorded on 300 MHz Bruker FT-NMR (Avance DPX300) spectrometer at 300 MHz for the ^1H and at 75.47 MHz for the ^{13}C nucleus. Chemical shifts are reported in ppm from TMS as the internal standard. Mass spectra were obtained on an ultraflex TOF/TOF MALDI mass spectrometer, which is equipped with a reflector and

controlled by the Flexcontrol1.4 software package. In MALDI-TOF MS reflector mode, ions generated by a pulsed UV laser beam (nitrogen laser $\lambda = 337$ nm, 20 Hz) were accelerated to a kinetic energy of 25 kV. TLC was performed on 0.2 mm Merck precoated silica gel 60 F254 aluminum sheets. All chromatographic purifications were carried out using silica gel 60 (60–120 mesh). All reagent chemicals were purchased from Aldrich Chemical Co (Milwaukee, WI, USA).

General Procedure for the O-tritylation/silylation Using Planetary Ball Mill

The substrate (**1/5/8/10/12**, 1 mmol), trityl chloride (**2**, 2.5 mmol) and DABCO (**3**, 2.5 mmol) were allowed to mix in a stainless steel [SS; material number, 1.4034, hardness, 48–52 HRC and composition (%), Fe (82.925), Cr (14.5), Mn (1), Si (1), C (0.5), P (0.045) and S (0.03)] jar (capacity, 50 mL) containing SS balls (10 numbers, 10 mm o.d.) for the desired period of time (as judged by TLC, see Tables 1–3) in a planetary ball mill (Retsch PM-100; Retsch GmbH & Co. KG, Germany) at the desired rpm (usually 500/600, see also Tables 1–3). The mixture was then purified on a silica gel column [eluent, EtOAc:*n*-Hex, 1:9 (to remove the by-products derived from excess **2**) and 4:1 successively] to yield the respective O-tritylated derivative, which was crystallized from EtOAc (or EtOAc:*n*-Hex) to obtain analytically pure product (**4/6/9/13/14**). Alternatively, as it had been possible in most of the cases studied, the product could also be obtained from the crude mixture directly by crystallization. The spectral data were in accordance with the expected structure and in agreement with literature values.

Methyl 6-O-trityl α -D-glucopyranoside⁽¹²⁾ (**4**)

This was prepared by the general procedure described above in 80% yield on 1-mmol scale reactions in the presence of DABCO at 500 rpm and 92–93% yield on 77-mmol scale reactions in the presence of Na₂CO₃ at 500/600 rpm, respectively, as white solid; NMR spectra were identical to those described.^[12a] mp 140°C (from EtOAc) (lit.^[2a] 138°C). MALDI-TOF MS C₂₆H₂₈O₆ [M]⁺ calcd. *m/z* 436.189, found *m/z* 475.805 (M + K⁺, 98%), 459.814 (M + Na⁺, 95%) and 243.537 (Tr⁺, 100%).

1,2:3,4-Di-O-isopropylidene-6-O-trityl- α -D-galactopyranose⁽¹⁶⁾ (**6**)

Prepared by the general procedure described above, this compound was purified by chromatography on a silica gel column using EtOAc:*n*-Hex = 1:9. Yield 59%; mp 77–78°C (lit.^[16a] 80–82°C); NMR spectra were identical to those described.^[16b] MALDI-TOF MS C₃₁H₃₄O₆ [M]⁺ calcd. *m/z* 502.236,

found m/z 541.657 ($M + K^+$, 57%), 525.679 ($M + Na^+$, 28%) and 243.419 (Tr^+ , 100%).

Cyclopentyl Trityl Ether⁽¹⁷⁾ (9)

Prepared by the general procedure described above, this compound was purified by chromatography on a silica gel column using EtOAc:*n*-Hex, 0.5:9.5 as the eluent. Yield 96%, syrup; ν_{max} (neat)/ cm^{-1} 3032, 3057, 2955, 2868, 1490, 1448, 1047, and 705; δ_H ($CDCl_3$) 7.47 (d, 6H, J 7.4, ArH), 7.28–7.17 (m, 9H, ArH), 4.01 (m, 1H, Cyclopent), 1.58 (m, 2H, Cyclopent), and 1.45–1.28 (m, 6H, Cyclopent); MALDI-TOF MS $C_{24}H_{24}O$ $[M]^+$ calcd. m/z 328.183, found m/z 351.621 ($M + Na^+$, 58%) and 243.631 (Tr^+ , 100%).

5'-O-Trityluridne⁽¹⁹⁾ (13)

Prepared by the general procedure described above, this compound was purified by chromatography on a silica gel column using EtOAc:*n*-Hex = 9:1. Yield 43%; mp 207–208°C (lit.^[2c] 200°C); NMR spectral data were identical to those described.^[19] MALDI-TOF MS $C_{28}H_{26}N_2O_6$ $[M]^+$ calcd. m/z 486.179, found m/z 525.729 ($M + K^+$, 4%), 509.746 ($M + Na^+$, 28%) and 243.489 (Tr^+ , 100%).

5'-O-(4,4'-Dimethoxytrityl)uridne⁽²⁰⁾ (14)

This was prepared by the general procedure described above, and purified by chromatography on a silica gel column using EtOAc:*n*-Hex = 9:1. Yield 44%; mp 111–112°C (lit.^[20a] 123–124°C); NMR spectral data were identical to those described.^[20b] MALDI-TOF MS $C_{30}H_{30}N_2O_8$ $[M]^+$ calcd. m/z 546.200 found m/z 585.172 ($M + K^+$, 0.02%), 569.191 ($M + Na^+$, 0.02%), 546.195 (M^+ , 0.004%), and 303.155 (DMT^+ , 100%).

General Procedure for the O-tritylation/silylation Followed by the Per-O-acetylation in One Pot Using Planetary Ball Mill

The substrate (1/16/18/20/22, 1 mmol), trityl- (or the desired silyl-) chloride (2, 2.5 mmol), and DABCO (3, 2.5 mmol) were allowed to mix in an SS jar (capacity, 50 mL) containing SS balls (10 numbers, 10 mm o.d) for the desired period of time (as judged by TLC, see Table 3) in a planetary ball mill at 500/600 rpm. To the crude O-tritylated product thus obtained DMAP (1 mmol) and Ac_2O (1.5 mol equiv per OH group to be acetylated) were added and the homogenization was continued for 30 min at 500 rpm. The resulting material was then taken up in CH_2Cl_2 and was subjected to an aq. workup

in a separatory funnel [successive washing with: i, cold dil aq HCl (20 mL \times 2); ii, aq 10% NaHCO₃ (20 mL \times 2); and iii, 50 mL water]. The organic solution was then dried (Na₂SO₄), separated by filtration at the pump, and concentrated to dryness under reduced pressure. The residue was purified on a silica gel column (eluent, EtOAc:*n*-Hex, 1:9) to yield the respective fully protected carbohydrates (**15a/15b/15c/17/19/21/23**) (see Table 3). Spectral data were in accordance with the expected structure and in agreement with literature values.

Methyl 2,3,4-tri-O-acetyl-6-O-trityl- α -D-glucopyranoside⁽¹³⁾ (15a)

This was prepared by the general procedure described above and isolated as colorless crystals. Yield 72%; mp 136°C (lit.^[2a] 136°C); NMR spectra were identical to those described.^[13a] MALDI-TOF MS C₃₂H₃₄O₉ [M]⁺ calcd. *m/z* 562.220, found *m/z* 601.961 (M + K⁺, 98%), 585.949 (M + Na⁺, 94%), and 243.590 (Tr⁺, 100%).

Methyl 2,3,4-tri-O-acetyl-6-O-*tert*-butyldiphenylsilyl- α -D-glucopyranoside⁽²¹⁾ (15b)

Compound **15b** was prepared by the general procedure described above in 71% yield as colorless solid; mp 82–83°C; NMR spectral data were identical to those described.^[21a] MALDI-TOF MS C₂₉H₃₈O₉Si [M]⁺ calcd. *m/z* 558.229, found *m/z* 597.809 (M + K⁺, 95%) and 581.822 (M + Na⁺, 100%).

Methyl 2,3,4-tri-O-acetyl-6-O-*tert*-butyldimethylsilyl- α -D-glucopyranoside⁽²²⁾ (15c)

This was prepared by the general procedure described above in an isolated yield of 49% as syrup; [α]_D = +110.3 (1 in CHCl₃) (lit.^[22a] +124); NMR spectral data were identical to those described.^[22b] MALDI-TOF MS C₁₉H₃₄O₉Si [M]⁺ calcd. *m/z* 434.197, found *m/z* 473.667 (M + K⁺, 20%), 457.692 (M + Na⁺, 35%) and 403.648 (M-OCH₃⁺, 100%).

Methyl 2,3,4-tri-O-acetyl-6-O-trityl- β -D-galactopyranoside⁽²³⁾ (17)

Compound **17** was prepared by the general procedure described above in 80% yield as colorless solid, mp 68–69°C (lit.^[23a] 143–145°C); [α]_D = –45.5 (lit.^[23a] –52.7); NMR spectra were identical to those described.^[23b] MALDI-TOF MS C₃₂H₃₄O₉ [M]⁺ calcd. *m/z* 562.220, found *m/z* 601.838 (M + K⁺, 43%), 585.851 (M + Na⁺, 49%), and 243.501 (Tr⁺, 100%).

2-(Trimethylsilyl)ethyl 2,3,4-tri-O-acetyl-6-O-trityl- β -D-galactopyranoside (19)

Compound **19** was prepared by the general procedure described above in 85% yield as white solid; mp 68–69°C; $[\alpha]_D = -41.9$ (C 1 in CHCl_3); ν_{max} (KBr)/ cm^{-1} 3033, 2952, 2890, 1754, 1449, 1368, 1249, 1221, 1079, and 707; δ_{H} (CDCl_3) 7.37 (d, 6H, J 7.0 Hz, ArH), 7.32–7.24 (m, 9H, ArH), 5.55 (d, 1H, $J_{3,4}$ 2.2 Hz, H-4), 5.13 (dd, 1H, $J_{1,2}$ 7.6 Hz and $J_{2,3}$ 10.2 Hz, H-2), 5.06 (dd, 1H, H-3), 4.45 (d, 1H, H-1), 3.97 (m, 1H, OCH_2), 3.79 (t, 1H, H-5), 3.52 (m, 1H, OCH_2), 3.39 (dd, 1H, $J_{5,6a}$ 5.5 Hz and $J_{6a,6b}$ 8.6 Hz, H-6a), 3.10 (t, 1H, H-6b), 2.04, 1.99, 1.89 (3s, 9H, 3 \times COCH_3), 0.94 (m, 2H, SiCH_2), and 0.00 (s, 9H, $\text{Si}(\text{CH}_3)_3$); MALDI-TOF MS $\text{C}_{36}\text{H}_{44}\text{O}_9\text{Si}$ $[\text{M}]^+$ calcd. m/z 648.275, found m/z 687.311 (M + K^+ , 46%), 671.321 (M + Na^+ , 73%) and 243.175 (Tr^+ , 100%).

Phenyl 2,3,4-tri-O-acetyl-6-O-trityl-1-thio- β -D-galactopyranoside (21)

Compound **21** was prepared by the general procedure described above in 82% yield as a white solid; mp 138°C; $[\alpha]_D = -10.2$ (C 1 in CHCl_3); ν_{max} (KBr)/ cm^{-1} 2925, 2876, 2854, 1752, 1440, 1368, 1265, 1252, 1217, 1082, 1057, and 706; δ_{H} (CDCl_3) 7.50 (m, 2H, ArH) 7.39 (m, 6H, ArH), 7.31–7.20 (m, 12H, ArH), 5.48 (d, 1H, $J_{3,4}$ 3.0 Hz, H-4), 5.19 (t, 1H, $J_{2,3}$ 9.9 Hz, H-2), 5.02 (dd, 1H, H-3), 4.71 (d, 1H, H-1), 3.72 (t, 1H, H-5), 3.43 (dd, 1H, $J_{5,6a}$ 6.2 Hz and $J_{6a,6b}$ 9.4 Hz H-6a), 3.08 (dd, 1H, H-6b), 2.08, 1.96, and 1.90 (3s, 9H, 3 \times COCH_3); MALDI-TOF MS $\text{C}_{37}\text{H}_{36}\text{O}_8\text{S}$ $[\text{M}]^+$ calcd. m/z 640.213, found m/z 679.905 (M + K^+ , 48%), 663.901 (M + Na^+ , 46%) and 243.507 (Tr^+ , 100%).

Methyl 3,4-di-O-acetyl-6-O-trityl-2-deoxy-2-phthalimido-1-thio- β -D-glucopyranoside (23)

Compound **13** was prepared by the general procedure described above in 39% yield as colorless solid; mp 83–84°C; $[\alpha]_D = +57.8$ (C 1 in CHCl_3); ν_{max} (KBr)/ cm^{-1} 2929, 1747, 1718, 1383, 1233, 1093, 1038, and 715; δ_{H} (CDCl_3) 7.87 (m, 2H, ArH), 7.74 (m, 2H, ArH), 7.47 (d, 6H, J 8.0 Hz, ArH), 7.33–7.21 (m, 9H, ArH), 5.82 (t, 1H, $J_{2,3}$ 9.4 Hz, H-3), 5.37 (d, 1H, $J_{1,2}$ 9.8 Hz, H-1), 5.28 (t, 1H, H-2), 4.49 (t, 1H, $J_{3,4}$ 9.4 Hz and $J_{4,5}$ 10.4 Hz, H-4), 3.82 (m, 1H, H-5), 3.31 (d, 1H, $J_{6a,6b}$ 10.5 Hz, H-6a), 3.14 (dd, 1H, $J_{5,6b}$ 4.0 Hz and $J_{6a,6b}$ 10.2 Hz H-6a), 2.25 (s, 3H, SCH_3), 1.85 and 1.74 (2s, 6H, 2 \times COCH_3); MALDI-TOF MS $\text{C}_{38}\text{H}_{35}\text{NO}_8\text{S}$ $[\text{M}]^+$ calcd. m/z 665.208, found m/z 704.209 (M + K^+ , 63%), 688.225 (M + Na^+ , 100%), and 243.122 (Tr^+ , 92%).

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