Solvent-controlled regioselective protection of allyl-4,6-benzylidene glucopyranosides
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Abstract
We wish to report a simple synthetic procedure, which permits the regiospecific mono-acylation, alkylation and silylation at the 2-position of allyl 4,6-O-benzylidene α-D-glucopyranoside in high yields and which does not require the use of catalysts.

Background
Numerous syntheses of oligosaccharides incorporating glucose moieties have been reported. In most cases, a limiting synthetic factor is the number of functional group manipulations required to access suitable synthetic precursors. For hexopyranoses, acylation of cis-diols can be achieved with high regioselectivity either by means of metal activators such as tin, [1-3] silver, [4] boron[5] or copper [6] or by exploiting the relative reactivity of hydroxyl groups [7,8] However, metal-promoted alkylation and base-catalysed acylation of diols have proven to be highly dependable in the case of glucose and other cyclic trans-diols, where both hydroxyl groups are equatorial. For instance, reports of identical procedures describing the tin-catalysed benzylation of methyl 4,6-O-benzylidene glucopyranoside claim isolated yields ranging from the 37% and below [9] to 75% and above [10] Others reported multi-step procedures to achieve introduction of a suitable protecting group at the 2-position of the 4,6-O-benzylidene 1-O-alkyl protected glucose [11] or used enzymes to achieve selectivity[12]

Results and discussion
While preparing the partially protected glucose 1 from α-allyl-4,6-benzylidene glucoside 2 (Scheme 1), we observed that mono-benzylation could be achieved, if instead of DMF and the usual reagents' combination (i.e. NaH, BnBr, Bu₄NI), THF was to be used as reaction solvent (Scheme 1). Osborn had reported the regioselective mono-acylation/alkylation of the C-3 hydroxyl of 4,6-O-benzylidene-β-D-glycopyranosides using NaH/CuCl₂ in THF[6] Distinctively, we observed the regioselective benzylation at the C-2 position of the 1-O-allyl-α-glucoside 2 (Scheme 2). This assignment was in agreement with previously published NMR data [11,13] and confirmed by acetylation of the mono-protected material 3d, to give compound 4, which resulted in an H-3 NMR shift from 4.15 ppm to 5.51 ppm.

Scheme 1: Target partially protected sugar 1.
Introduction of other protecting groups were then considered. Alkylation, acylation and silylation using halogenated reagents offered mono-protection when reactions were carried out in THF and regio-selectivity was achieved when large protecting groups were employed (Table 1) (see Additional File 1 for full experimental data). In most cases, the expected products could not be obtained when DMF was used as solvent.

Two conclusions could be drawn. Firstly, mono-alkylation of allyl 4,6-O-benzylidene α-D-glucopyranoside could be achieved in THF under concentrated solution conditions, even in the presence of an excess of base and alkylating reagent. Secondly, regioselectivity was achieved if the alkylating reagent was bulky (Table 1). When both allyl bromide and acetyl chloride were used for the reaction in THF a mixture of the C-2 and C-3 mono-protected products were formed. The smaller protecting groups do not encounter the same steric hindrance as the larger

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**Table 1: Reaction of 2 with alkylating, acylating and silylating reagents and products distribution.**

| Product type | Reagent | Conditions | A or B | Crude yield | 2 isolated yield | 3 isolated yield | 5 isolated yield | 6 isolated yield |
|--------------|---------|------------|--------|-------------|-----------------|-----------------|-----------------|-----------------|
| a | CH₃COCl | THF | 98 | 22 | 36 | 36 | - |
| a | CH₃COCl | DMF | 99 | 20 | - | - | 75 |
| b | CH₂=CHCH₂Br | THF | 95 | 25 | 31 | 31 | - |
| b | CH₂=CHCH₂Br | DMF | 97 | 26 | - | - | 64 |
| c | H₂C=CH₂Br | THF | 89 | 21 | 43 | 32 | - |
| c | H₂C=CH₂Br | DMF | 90 | 26 | - | - | 68 |
| d | BnBr | THF | 93 | 23 | 68 | - | - |
| d | BnBr | DMF | 95 | 22 | - | - | 76 |
| e | PhCOBr | THF | 92 | 32 | 57 | - | - |
| e | PhCOBr | DMF | 97 | 28 | - | - | 62 |
| f | PMBCl | THF | 94 | 30 | 56 | - | - |
| f | PMBCl | DMF | 85 | 34 | - | - | 63 |
| g | TBDMSCl | THF | 88 | 23 | 52 | - | - |
| g | TBDMSCl | DMF | 92 | 92 | - | - | - |
| h | TBDPSiCl | THF | 97 | 48 | 45 | - | - |
| h | TBDPSiCl | DMF | 96 | 96 | - | - | - |
| i | TMSCl | THF | 96 | 44 | 50 | - | - |
| i | TMSCl | DMF | 97 | 97 | - | - | - |

* A: THF; 70°C, 16 hours, 3.5 eq RCl, 4.5 eq NaH, Bu₄NI, 0.024 M; B: DMF; 70°C, 16 hours, 3.5 eq RCl, 4.5 eq NaH, 0.024 M.
Table 2: Reaction of galactoside 7 with alkylation and silylation reagents and products distribution.

| Product type | Reagent | Conditions a | Crude yield % | 7 isolated yield % | 8 isolated yield % | 9 isolated yield % | 10 isolated yield % |
|--------------|---------|--------------|---------------|-------------------|-------------------|-------------------|-------------------|
| a            | PMBCl   | THF          | 96            | 30                | -                 | -                 | 60                |
| a            | PMBCl   | DMF          | 95            | 20                | -                 | -                 | 75                |
| b            | TBDMScI | THF          | 92            | 15                | 38                | 35                | -                 |
| b            | TBDMScI | DMF          | 93            | 65                | -                 | -                 | -                 |
| c            | TBDPScl | THF          | 90            | 48                | 20                | 20                | -                 |
| c            | TBDPScl | DMF          | 85            | 68                | -                 | -                 | -                 |

* A: THF; 70°C, 16 hours, 3.5 eq RCl, 4.5 eq NaH, Bu4NI, 0.024 M; B: DMF; 70°C, 16 hours, 3.5 eq RCl, 4.5 eq NaH, 0.024 M.

Table 3: Reaction of glucoside 11 with benzyl halide and products distribution.

| Sugar | Conditions a | Crude yield % | 11 isolated yield % | 12 isolated yield % | 13 isolated yield % | 14 isolated yield % |
|-------|--------------|---------------|---------------------|---------------------|---------------------|---------------------|
| II    | THF          | 92            | 23                  | -                   | -                   | 64                  |
| II    | DMF          | 95            | 20                  | -                   | -                   | 68                  |

* A: THF; 70°C, 16 hours, 3.5 eq BnBr, 4.5 eq NaH, Bu4NI, 0.024 M; B: DMF; 70°C, 16 hours, 3.5 eq BnBr, 4.5 eq NaH, 0.024 M.

Table 4: Reaction of glucoside 15 and 16 with benzyl halide and products distribution.

| Product type | Sugar | Conditions a | Crude yield- % | 15 or 16 isolated yield % | 17 isolated yield % | 18 isolated yield % | 19 isolated yield % |
|--------------|-------|--------------|----------------|---------------------------|--------------------|--------------------|-------------------|
| a            | 15    | THF          | 87             | 26                        | -                  | -                  | 60                |
| a            | 15    | DMF          | 90             | 21                        | -                  | -                  | 70                |
| b            | 16    | THF          | 93             | 21                        | -                  | -                  | 68                |
| b            | 16    | DMF          | 95             | 19                        | -                  | -                  | 75                |

* A: THF; 70°C, 16 hours, 3.5 eq BnBr, 4.5 eq NaH, Bu4NI, 0.024 M; B: DMF; 70°C, 16 hours, 3.5 eq BnBr, 4.5 eq NaH, 0.024 M.
groups due to the benzylidene ring. Yet no bis-protected product is formed with these reagents under these conditions, suggesting that once one hydroxyl has reacted to give the mono-protected product, the other hydroxyl must be deactivated so that no further reaction occurs.

In order to rationalise such regioselectivity, alkylation and silylation reactions of other 4,6-benzylidene protected glycosides were carried out (Tables 2, 3, 4). The reaction carried out with DMF as solvent gave the bis-protected galactosides when PMBCl was used and no reaction when the silylating reagents were used. In THF, alkylation occurred with similar outcomes to that observed in DMF. However, THF offered means to access the monosilylated protecting group at the C-1 position, i.e. the allyl group.

In summary, we have stumbled on a very simple, yet very versatile and high yielding method to specifically protect the C2-hydroxyl group of α-allyl-glucoside, which does not require any form of activators. It can be anticipated that this method will share itself to the introduction of moieties other than protecting groups, such as hindered alkyl and silyl halides or acylchlorides of carbohydrate derivatives.

Additional material

Additional file 1

experimental section. The data provided describes the procedures employed to complete the synthetic work.

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