Highly Stereoselective α-Alkylations, 1,4-Additions, and One-pot 1,4-Addition/α-Methylations Achieved on 4-*O*-Acyl and 4-*O*-Crotonyl Derivatives of Methyl 6-Deoxy-2,3-di-*O*-(*t*-butyldimethylsilyl)-α-D-glucopyranoside

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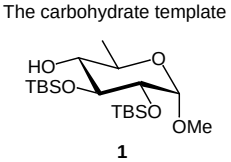
Abstract: Benzylation or methylation of the enolate generated from 4-*O*-propionyl or 4-*O*-3-phenyl-propionyl derivatives of methyl 6-deoxy-2,3-di-*O*-(*t*-butyldimethylsilyl)-α-D-glucopyranoside provided the respective C-alkylated product stereoselectively. The 1,4-additions of a variety of carbon nucleophiles to the corresponding 4-*O*-crotonyl derivative provided adducts with high and complementary diastereoselection. The one-pot 1,4-additions of a phenyl nucleophile to the 4-*O*-crotonyl ester followed by the addition of methyl iodide provided vicinally substituted products with high diastereo- and enantioselectivity, from which diastereomeric α-methyl-β-phenylbutanols were obtained in enantioenriched form after reductive removal of the carbohydrate template.

Key words: diastereoselectivity, carbohydrates, chiral auxiliaries, Michael-additions, alkylations

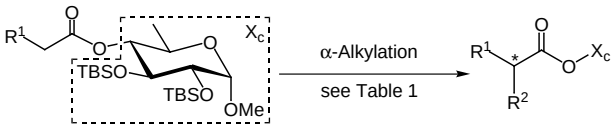
In the field of asymmetric synthesis, methods using asymmetric environments derived from natural products have been widely utilized.[1–3] In the last few years, we have explored the stereoselective carbon-carbon bond forming reactions achieved on some hexopyranosidic templates. We have reported the results of the 1,4-additions of organocopper reagents,[4,5] conjugate additions of alkyl radicals[6] and Diels–Alder reactions with cyclopentadiene[7] conducted on a variety of carbohydrate templates. In the past two decades, other groups have reported stereoselective carbon-carbon bond forming reactions using carbohydrate-induced asymmetric environments.[8] In this communication, we report highly stereoselective α-alkylations, 1,4-additions, and one-pot 1,4-addition/α-methylations achieved by using 4-*O*-acyl and 4-*O*-crotonyl derivatives incorporated into methyl 6-deoxy-2,3-di-*O*-(*t*-butyldimethylsilyl)-α-D-glucopyranoside **1** (Figure 1).[6,7]



1

Figure 1

We first conducted the α-alkylation of two 4-*O*-esters **2**[9,10] and **3**[10] prepared from **1** (Scheme 1). The results are shown in Table 1. After a variety of bases (LDA, LiHMDS, NaHMDS or KHMDS) and additives (HMPA or LiCl) were examined, the optimal reaction conditions were obtained when NaHMDS [sodium bis(trimethylsilyl)amide] was used as the base without any additive.[11] Benzylation (for **2**) and methylation (for **3**) provided the alkylation products **4S**[12] and **4R**, respectively, with useful levels of stereoselectivity. The stereoselectivity in the alkylation was determined accurately using chiral HPLC analysis of enantioenriched 2-methyl-3-phenylpropanol after reductive removal of the carbohydrate template from the alkylation product. We explain the observed stereochemical outcome using transition-state models as shown in Figure 2. Because of the unfavorable steric environment occurring between R^1 and the carbohydrate template, it is more likely to form the (*Z*)-enolate from both **2** and **3** as depicted as TS-A. In this case, the TBS group shields effectively the front side of the enolate. As a result, the electrophile attacks from the rear, leading to the α-alkylated products **4S** from **2** or **4R** from **3**.[13]



2: R^1=Me, **3**: R^1=CH_2Ph **4**: R^1, R^2=Me, CH_2Ph

Scheme 1

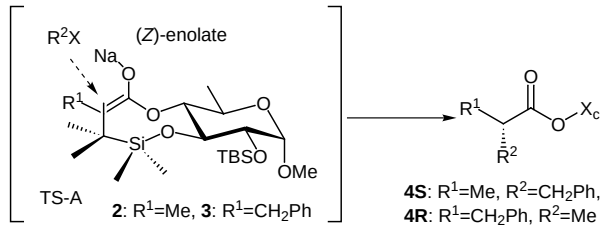


Figure 2 Plausible transition-state models for the α-alkylations of substrates **2** and **3**

Next, we investigated the 1,4-additions of three organocopper reagents or three organolithiums to **5**,[6] the 4-*O*-crotonyl derivative of **1** (Scheme 2). We examined ethyl-, *t*-butyl-, and phenylcopper reagents prepared from

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1437-2096,E;2001,0,11,1772,1776,ftx,en;Y16901ST.pdf.

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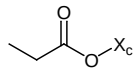
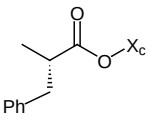
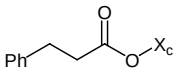
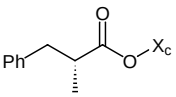
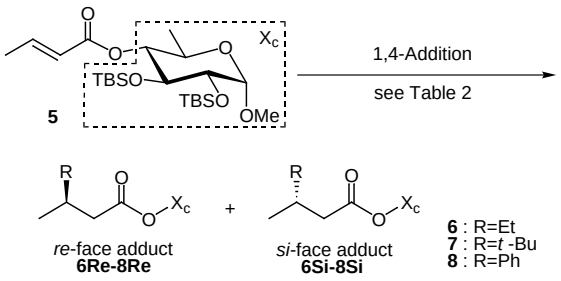
Table 1 α-Alkylations[a] of Substrates **2** and **3**

Entry	Substrate	RX	Temp (°C)	Product	Yield (%)[c,d]	Stereoselectivity[e]
1	 **2**	BnBr	–78 to –18	 **4S**[b]	97	95:5
2	 **3**	MeI	–78 to –18	 **4R**	80 (13)	98:2

[a] NaHMDS (1.2 equiv), RX (1.5 equiv), THF.
[b] Absolute configuration was determined by comparison of $[\alpha]_D$ value of (*S*)-2-methyl-3-phenylpropanol, obtained by reductive removal of the carbohydrate template, to the reported value for the (*R*)-isomer.
[c] Yields for mixture of diastereoisomers.
[d] Yield in parenthesis is that for recovered starting material.
[e] Stereoselectivity was determined by chiral HPLC analysis of enantioenriched 2-methyl-3-phenylpropanol. Retention times for (*S*)-2-methyl-3-phenylpropanol, 28.4 min; for the (*R*)-isomer, 34.6 min (serial connection of DAICEL Chiralcel OD+ODH, 2-propanol/hexane=1:20).

the corresponding Grignard reagent and cuprous bromide-dimethyl sulfide.[14,15] The results of the 1,4-additions to **5** are summarized in Table 2. In the cases of the 1,4-additions using three organocopper reagents (entries 1–3), the adducts **6Re-8Re**[16] were obtained with high diastereoselectivities. The stereoselectivities in the 1,4-additions to **5** were determined by chiral HPLC analysis of the corresponding anilides, prepared from the respective 3-methylpentanoic acid (from **6Re**) or 3,4,4-trimethylpentanoic acid (from **7Re**) (aniline, WSCI, DMAP, CH_2Cl_2), or by chiral HPLC analysis of 3-phenylbutanol prepared from **8Re** by the reductive removal of the carbohydrate template **1**. We also examined the 1,4-additions of the corresponding organolithiums[17] to **5** (Table 2, entries 4–6). These reactions completed at –78 °C to provide the respective 1,4-adducts with high yields and high diastereoselectivities.[18] In all cases, the major adducts **6Si-8Si** were obtained as a result of *si*-face attack of the organolithium. Although we have no evidence, the stereochemical reversals observed in entries 1–3 to 4–6 may be explained by conformational change of the crotonyl ester moiety. In the cases of the 1,4-additions using excess organocopper reagents (entries 1–3), the organocopper reagents or magnesium halide coordinated with the crotonyl carbonyl group. This caused a steric hindrance between the coordinated metal species and the carbon-carbon double bond, which made the *s-trans, syn* conformation[19] of the crotonyl ester moiety more favorable (Figure 3).[20] On the other hand, the organolithium did not tend to coordinate with the crotonyl carbonyl. Consequently, the organolithium attacked the β-carbon of the crotonyl ester from less-hindered side in the *s-cis, syn* conformation (entries 4–6). This conformational change of the crotonyl ester moiety resulted in the reversal of the π-face hindered by the bulky *t*-butyldimethylsilyloxy group at C-3.[21]



Scheme 2

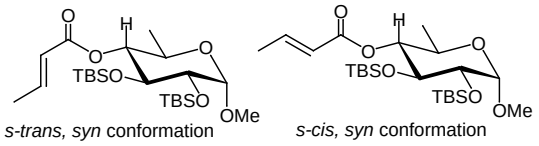


Figure 3

Finally, we carried out one-pot 1,4-addition/α-methylations[22] with the expectation of effective asymmetric induction at both the α- and β-positions of the crotonyl ester in **5**. The aforementioned 1,4-additions of the phenylcopper reagent[23] or phenyllithium[23] to **5** followed by the addition of methyl iodide proceeded with high diastereoselectivity to provide the adducts **9**-syn[24] or **9**-anti,[24] carrying a 2-methyl-3-phenylbutanoic acid at C-4 in **1** (Table 3). We also conducted the α-methylation of **8Re** and **8Si**. As a result, **9**-syn and **9**-anti, respectively, were obtained as the predominant products.[25] The configurations of the α-carbon in the products **9**-syn and **9**-anti were the same (*S*)-configuration. From this fact, we speculate that the configurations of the enolates generated after 1,4-additions to **5** of both two phenyl metallic species are same. The enolates are likely to exist as *E*-enolates more

Table 2 1,4-Additions of R_2CuMgX or RLi to **5**

Entry	R	Method[a]	Temp. (°C)	Yield (%)[b,c]	Major Product	Stereoselectivity[d]
1	Et	a	–78 to –18	85	**6Re**	95:5
2	*t*-Bu	a	–78 to 0	58 (30)	**7Re**	92:8
3	Ph	a	–78 to 0	85	**8Re**	95:5
4	Et	b	–78	92	**6Si**	96:4
5	*t*-Bu	b	–78	95	**7Si**	98:2
6	Ph	b	–78	92	**8Si**	97:3

[a] Method a: CuBr·Me_2S (5 equiv), EtMgBr, *t*-BuMgCl or PhMgBr (10 equiv), THF–Me_2S (2:1). Method b: RLi (1.5 equiv), THF.
[b] Yields for mixture of diastereoisomers.
[c] Yield in parenthesis is that for recovered starting material.
[d] Stereoselectivity was determined by HPLC analysis of the corresponding enantioenriched anilides or 3-phenylbutanol. Retention times of 3-methylpentananilide (from **6Re** and **6Si**): for (*S*)-isomer, 26.5 min, for (*R*)-isomer, 28.3 min (DAICEL Chiralcel ODH, EtOH/hexane=1:30). Retention times of 3,4,4-trimethylpentananilide (from **7Re** and **7Si**): for (*R*)-isomer, 22.1 min, for (*S*)-isomer, 37.5 min (DAICEL Chiralcel OD, 2-propanol/hexane=1:10). Retention times of 3-phenylbutanol (from **8Re** and **8Si**): for (*R*)-isomer, 11.3 min, for (*S*)-isomer 12.6 min (DAICEL Chiralcel ODH, 2-propanol/hexane=1:10).

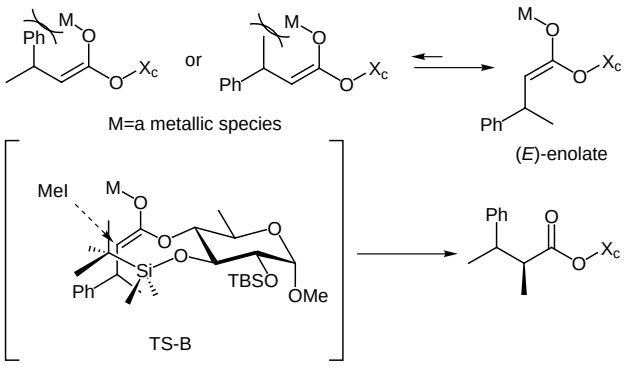
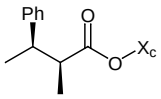
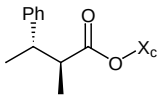


Figure 4 Plausible transition-states models for 1,4-addition/α-alkylation of **5**

favorably from the standpoint of steric repulsion as shown in Figure 4. The methyl iodide attacks from the less-congested rear side to provide **9**-syn and **9**-anti as shown in TS-B.

In summary, we have found highly diastereoselective α-alkylations, 1,4-additions, and one-pot 1,4-addition/α-methylations achieved on the hexopyranosidic esters **2**, **3**, or **5**. In particular, the 1,4-additions to **5** using organocopper reagents or organolithiums revealed the complementary results. All products obtained by the alkylations and additions were transformed into chiral alcohol or carboxylic acids possessing high optical purities by the removal of the carbohydrate template.

Table 3 One-Pot 1,4-Addition/α-Alkylations to **5**

Entry	Method[a]	Major Product	Yield (%)[b,c]	Stereoselectivity
1	a	 **9**-syn	52 (39)	*syn*:*anti* =94:6[d] e.r. of *syn*-2-methyl-3-phenylbutanol =>99:1[e]
2	b	 **9**-anti	92	*anti*:*syn* =>95:5[d] e.r. of *anti*-2-methyl-3-phenylbutanol =>99:1[e]

[a] Method a: CuBr·Me_2S (5 equiv), PhMgBr (10 equiv), THF–Me_2S (2:1), –18 °C to 0 °C then MeI (20 equiv). Method b: PhLi (2 equiv), THF, –78 °C then MeI (4 equiv).
[b] Yields for mixture of diastereoisomers.
[c] Yield in parenthesis is for **8Re**.
[d] Determined by ^1H NMR analysis of the mixture of *syn*- and *anti*-2-methyl-3-phenylbutanol, prepared by removal of the carbohydrate template.
[e] Retention times of (2*S*, 3*R*)- and (2*S*, 3*S*)-2-methyl-3-phenylbutanol, prepared from **9**-syn and **9**-anti, respectivery: for (2*S*, 3*R*)-isomer, 25.7 min, for (2*S*, 3*S*)-isomer, 20.7 min (DAICEL Chiralcel ODH, 2-propanol/hexane=1:50).

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(9) All new compounds were fully characterized by ^{1}H and ^{13}C NMR, IR and HRMS after chromatographic purification on silica gel.

(10) The 4-*O*-acyl derivatives **2** and **3** were prepared from **1**. For **2**: $(CH_3CH_2CO)_2O$, DMAP, pyr., 80 °C (98%). For **3**: LiHMDS, $PhCH_2CH_2C(O)Cl$, Et_2O, –78 °C (83%, 15% recovery of **1**).

(11) A typical procedure for the α-benzylation of 4-*O*-propionyl ester **2**: To a cooled (–78 °C) solution of **2** (47.5 mg, 0.103 mmol)in THF (1 mL) was added NaHMDS (1.0 M solution in THF, 0.11 mL, 0.11 mmol). The solution was stirred at -78 °C for 15 min, then BnBr (18.5 μL, 0.156 mmol) was added. After being stirred at -78 °C for 15min, then at –18 °C for 15 min, the reaction mixture was quenched with sat. aq. NH_4Cl. The mixture was diluted with EtOAc (10 mL) and washed with sat. aq. NH_4Cl (5 mL × 3). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (toluene) to give 55.1 mg (97%) of an inseparable mixture of **4S**/**R** as a colorless oil (e.r. of the corresponding 2-methyl-3-phenylpropanol = 95:5, chiral HPLC analysis).

(12) The configuration of the newly introduced stereogenic carbon in **4S** was determined to be *S* by comparing the $[\alpha]_D$ sign of 2-methyl-3-phenylpropanol {$[\alpha]^{19}_D$ –10.7 (c 0.64, benzene)}, obtained by the reductive removal (DIBAL-H, CH_2Cl_2, –78 °C to –18 °C) of the carbohydrate template **1** from **4S**, to the reported sign for (*R*)-2-methyl-3-phenyl-propanol {$[\alpha]_D$+11.0 (c 1.15, benzene)}, see: Ref. 2a.

(13) We tried to trap the enolate formed from **2** (NaHMDS, THF, –78 °C to –18 °C) with TBSCl or TMSCl to verify the geometry of the enolate. In both cases, unfortunately, we could not obtain the silylated enolate. The substrate **2** was recovered quantitatively after quenching with water.

(14) For a typical procedure for the 1,4-addition of an organocopper reagent to structurally resembling glucopyranosidic templates, see Refs 4 and 5.

(15) The 1,4-addition to **5** of the phenyl Grignard reagent in the absence of $CuBr{\cdot}Me_2S$ provided the corresponding 1,2-addition product in a reduced yield.

(16) The absolute configurations of the newly introduced stereogenic carbon (β-carbon) in the major adducts **6Re** and **7Re** were determined by comparing the sign of 3-methyl-pentanoic acid (from **6Re**)or 3,4,4-trimethylpentanoic acid (from **7Re**), obtained by the hydrolytic removal of the carbohydrate template, with the reported $[\alpha]_D$ data.6 The absolute configuration of the β-carbon in **8Re** was determined to be **R** by comparing the $[\alpha]_D$ sign of enantioenriched 3-phenylbutanoic acid {$[\alpha]^{23}_D$ –44.4 (c 1.4, benzene)}, prepared from **8Re** by the hydrolytic removal of **1**, to that for the known (*R*)-enantiomer {$[\alpha]^{20}_D$ –51 (c 1, benzene)}, see: Grimshaw, J.; Millar, P. G. *J. Chem. Soc. (C)* **1970**, 2324.

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(18) The 1,4-addition of phenyllithium to **5** (entry 6): To a cooled (–78 °C) solution of **5** (156 mg, 0.329 mmol) in THF (3 mL) was added PhLi (1.04 M solution in cyclohexane–ether, 0.48 mL, 0.499 mmol). After being stirred at -78 °C for 15 min, the solution was quenched with sat. aq. NH_4Cl. The mixture was diluted with EtOAc (10 mL) and washed with sat. aq. NH_4Cl (5 mL × 3). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:70) to give 167 mg (92%) of an inseparable mixture of **8Si**/**Re** as a colorless oil (e.r. of 3-phenylbutanol = 97:3, chiral HPLC analysis).

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(24) The structures of 9-syn and 9-anti were determined based on comparison of the ^{1}H NMR data of syn- and anti-2-methyl-3-phenylbutanols with the reported data for racemates. These enantioenriched syn- and anti-2-methyl-3-phenylbutanol were prepared from 9-syn and 9-anti by the removal of the carbohydrate template 1 (DIBAL-H, CH_2Cl_2, –78 °C to –18 °C). Their enantiopurities were determined by chiral HPLC analysis. For the 1H NMR data of (2SR, 3RS)-syn- and (2SR, 3SR)-anti -2-methyl-3-phenylbutanol, see: Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10695.

(25) The α-methylation of **8Re** (d.r = 95:5) [NaHMDS, MeI, –18 °C to 0 °C, THF] provided **9**-syn in 84% yield (*syn*:*anti* = 95:5; e. r. of *syn* -2-methyl-3-phenylbutanol = >99:1). Analogously, α-methylation of **8Si** (d.r. = 97:3), under the same reaction conditions used for **8Re**, provided **9**-anti in 76% yield (20% recovery of **8Si**) (*anti*:*syn* = 94:6; e.r. of *anti*-2methyl-3-phenylbuanol =>99:1).