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Note

Regioselective ring opening of benzylidene acetal protecting group(s) of hexopyranoside derivatives by DIBAL-H

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ABSTRACT

The reductive ring-opening reaction of benzylidene-protected glucosides and mannosides such as methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucoside (**1**) and methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannoside (**4**) by using a toluene stock solution of DIBAL-H and a dichloromethane stock solution of DIBAL-H gives mainly or selectively the corresponding 2,3,4-tri-*O*-benzyl derivatives (**2**, **5**) and 2,3,6-tri-*O*-benzyl derivatives (**3**, **6**), respectively, although that of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactoside (**7**) gives methyl 2,3,6-tri-*O*-benzyl-α-D-galactoside (**9**) selectively irrespective of the solvent of the stock solution of DIBAL-H. Similarly, the reaction of the *exo*-isomer of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranosides (*exo*-**10**) with a toluene stock solution and dichloromethane stock solutions of DIBAL-H selectively gives methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannoside (**12**) and methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannoside (**11**), respectively, although that of *endo*-**10** selectively affords **11**, irrespective of the solvent of the stock solution of DIBAL-H.

It is well known that carbohydrates play important roles, not only as partial structures of various biologically active natural compounds, but also as inexpensive chiral sources for the synthesis of many chiral compounds.[1] The selective protection of hydroxy groups is necessary for organic synthesis utilizing carbohydrates, because carbohydrates are not generally soluble enough in organic solvents to cause chemo-, regio-, and stereoselective chemical reactions. Hung and co-workers have recently reported an excellent method to prepare many selectively protected carbohydrates by the 'regioselective one-pot protection of carbohydrates' in which the corresponding methyl 2,3,4,6-tetra-*O*-trimethylsilylpyranosides were used as starting materials.[2] However, one selective protection method for hydroxy groups, the regioselective reductive ring opening of 4,6-*O*-benzylidene acetals in 4,6-*O*-benzylidenehexopyranosides, has been shown to give either the corresponding 4-*O*-benzyl-6-hydroxy[3] or 6-*O*-benzyl-4-hydroxy[4,3e] derivative with high selectivity and in good yield. For example, Mitsunobu and co-workers[3a] first reported that DIBAL-H was useful for the selective conversion of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucoside (**1**) to methyl 2,3,4-tri-*O*-benzyl-α-D-glucoside (**2**) [with a minor amount of methyl 2,3,6-tri-*O*-benzyl-α-D-glucoside (**3**)] in dichloromethane as reaction solvent. Unfortunately, the kind of solvent of the stock solution of DIBAL-H was not described.

Alternatively, there are several other methods for the highly selective conversion of **1** to **2** or **3**, although the reason for the difference in the selectivity of these reactions is not yet clear. It is thought to be due to the particular reaction conditions such as the kind of Lewis acid and reaction solvent employed as well as the reducing reagents, as shown in Scheme 1.

Oscarson and co-workers[3h] reported a difference of selectivity due to the reaction solvent in the reductive opening of 4,6-*O*-benzylidene acetals derived from glucose and galactose. For example, the reaction of **1** with $BH_3{\cdot}Me_3N{-}AlCl_3$ in THF and in toluene selectively gave **3** (71%) and **2** (50%), respectively. Kusumoto and co-workers[3g] also reported an effect of solvent in the reductive opening of 4,6-*O*-benzylidene acetals derived from glucose and glucosamine, in which **1** was treated with $BH_3{\cdot}Me_2NH{-}BF_3{\cdot}OEt_2$ in acetonitrile and in dichloromethane to give **2**:**3** = 55%:30% and **2**:**3** = 73%:3%, respectively.

During our study on the preparation of protected glucopyranosides as chiral building blocks for the synthesis of optically active compounds, we found that the regiochemistry of the reductive ring opening of benzylidene acetal **1** depends heavily on the solvent in which the stock solution of DIBAL-H is prepared. Thus, a *dichloromethane stock solution of DIBAL-H* gave mainly **3**, while **2** was the main product from treatment of **1** with a *toluene stock solution of DIBAL-H*. Typical results are shown in Table 1.

Regardless of the kind of reaction solvent, the reduction of **1** by DIBAL-H in dichloromethane (entries 1–8) and DIBAL-H in toluene in the absence of $Cu(OTf)_2$ (entries 9–12) gave **3** and **2** as the major products, respectively. It is noteworthy that the reduction of **1** with a toluene stock solution of DIBAL-H in the presence of a Lewis acid, such as $Cu(OTf)_2$, gave mainly **3** (entry 13). We also found that even

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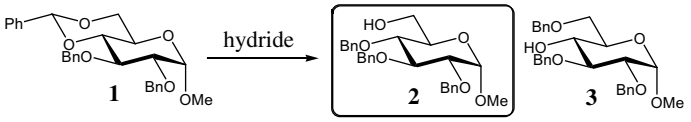


reagents (mol equiv.)	temp (°C)	time (min or h)	reaction solvent	yield (%) 2	yield (%) 3	reference
DIBAL-H (5)	-30	21 h	CH_2Cl_2	88	4	3(a)
LAH–$AlCl_3$ (4.75 / 4.06)	reflux	2 h	CH_2Cl_2-ether	94		3(b)
BH_3·THF–Bu_2BOTf (10 / 1)	0	1 h	CH_2Cl_2	87		3(c)
BH_3·THF–$CoCl_2$ (3 / 3)	rt	10 min	THF	quant		3(f)
BH_3·THF–$V(O)(OTf)_2$ (5 / 0.15)	rt	3 h	CH_2Cl_2	94		3(d)
BH_3·THF–$Cu(OTf)_2$ (5 / 0.05)	rt	2.5 h		95		3(e)
BH_3·Me_3N–$Cu(OTf)_2$ (5 / 0.05)	rt	25 h	CH_2Cl_2	0	40	3(e)
BH_3·Me_2NH–BF_3·OEt_2 (5 / 5)	0	<1 h	CH_2Cl_2	73	3	3(g)
BH_3·Me_3N–$AlCl_3$ (5 / 5)	rt		toluene	50		3(h)
BH_3·Me_3N–$AlCl_3$ (6 / 6)	rt		THF		71	3(h)
$NaCNBH_3$–HCl·OEt_2 (12.5 / ?)	rt	5 min	THF		81	4(a), 4(b)
Et3SiH–CF3CO2H (5 / 5)	0-rt	2–4 h	CH_2Cl_2		81	4(c)
Et3SiH–BF3·OEt_2 (12 / 2)	0-25	4 h	CH_2Cl_2		83	4(d)
Me_2EtSiH–$Cu(OTf)_2$ (2 / 0.01)	rt	0.5 h	CH_3CN	0	84	3(e)

Scheme 1. Selective cleavage of 4,6-*O*-benzylidene acetal **1** to 4-*O*-benzyl derivative **2** and 6-*O*-benzyl derivative **3**.

Table 1
Selective cleavage of 4,6-*O*-benzylidene acetal of **1** by DIBAL-H to give **2** and **3**[a]

Entry	DIBAL-H[b] solution (mol equiv)	Reaction solvent (M)	Temperature (°C)	Time (h)	Products (yield/%)[c] 2	3
1	CH_2Cl_2 (5.0)	CH_2Cl_2 (0.2)	−30	20.0	16	83
2	CH_2Cl_2 (3.0)	CH_2Cl_2 (0.2)	0	2.0	10	81
3	CH_2Cl_2 (2.2)	CH_2Cl_2 (0.2)	15	2.0	14	65
4	CH_2Cl_2 (3.0)	—	0	1.5	12	82
5	CH_2Cl_2 (3.0)	Toluene (0.2)	0	3.0	13	77
6	CH_2Cl_2 (3.0)[d]	CH_2Cl_2 (0.2)	0	1.5	16	53
7	CH_2Cl_2 (3.0)[e]	CH_2Cl_2 (0.2)	0	1.5	20	64
8	CH_2Cl_2 (3.0)[f]	CH_2Cl_2 (0.2)	0	1.5	16	79
9	Toluene (5.0)	CH_2Cl_2 (0.2)	−30	20.0	82	12
10	Toluene (3.0)	—	0	8.0	74	18
11	Toluene (3.0)	Toluene (0.2)	0	7.0	69	18
12	Toluene (3.0)	Toluene (0.2)	−10	1.5	91	Trace
13[g]	Toluene (3.0)	Toluene (0.2)	−10	5.0	23	72

[a] Reactions were performed by DIBAL-H (1 M solution in CH_2Cl_2 or toluene) with **1** (0.5 mmol, in toluene or CH_2Cl_2 solution (1 M), or solvent free.
[b] Purchased from Kanto Chemical Co. and kept in the refrigerator at 10–15 °C for over one year.
[c] After isolation by column chromatography on silica gel.
[d] Two weeks after preparation of the solution from neat DIBAL-H purchased from TOSOH FINECHEM CO. and dry CH_2Cl_2 distilled over CaH_2.
[e] Two months after the preparation of DIBAL-H solution.
[f] Five months after the preparation of DIBAL-H solution.
[g] Reaction was performed in the presence of $Cu(OTf)_2$ (5 mol %).

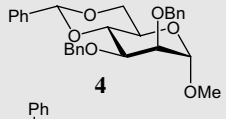
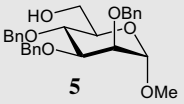
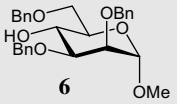
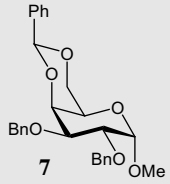
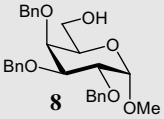
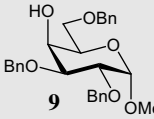
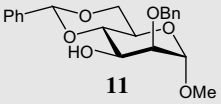
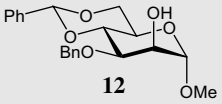
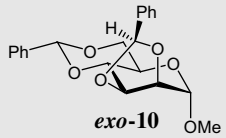
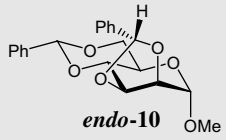
the use of a freshly prepared DIBAL-H solution in dichloromethane resulted in formation of **3** as the major product. The age of the DIBAL-H solution did not significantly affect the product selectivity (entries 6–8). These results clearly show that product selectivity, specifically the direction of the bond cleavage in **1**, depends on the solvent in which the stock solution of DIBAL-H is prepared. Ultrasonication of the fresh dichloromethane solution of DIBAL-H for few hours was not effective in increasing the selectivity.

This finding prompted us to investigate whether such a solvent effect is observed in the reductive ring opening of benzylidene acetals of some easily available hexopyranosides with DIBAL-H. Typical results are summarized in Table 2.

Similar results were again observed in the reaction of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannoside **4** (entries 1 and 2). The direction of ring opening of 4,6-*O*-benzylidene acetal **4** was the same as that observed in **1** and depended on the DIBAL-H solvent. This is a rare example of obtaining **6** selectively and in good yield. For example, Hung and co-workers[3e] described that **6** was obtained selectively in 70% yield by treatment with Me_2EtSiH (2 equiv) in the presence of $Cu(OTf)_2$ (1 mol %), and Debenham and Toone[4d] also reported that the use of Et_3SiH (12 equiv) gave **6** selectivity in 83% yield in the presence of BF_3·OEt_2 (2 equiv). On the other hand, Lipták and co-workers[3b] reported that LAH (5 equiv) served as an effective reagent in the presence of $AlCl_3$ (4 equiv) to give **5** (86%) highly regioselectively. Sato and co-workers[3f] described that BH_3·THF (3 equiv) was effective for regioselective ring opening of the 4,6-*O*-benzylidene acetal of **4** to give **5** in the presence of $CoCl_2$ (3 equiv). Hung and co-workers also reported a regioselective ring-opening reaction of **4** with BH_3·THF (5 equiv) in the presence of $V(O)(OTf)_2$ (15 mol %)[3d] and $Cu(OTf)_2$ (5 mol %)[3e] to give **5** in 91% and 84%, respectively.

In the case of methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactoside (**7**), however, no difference in the direction of ring opening was observed using either dichloromethane or toluene solutions of DIBAL-H (entries 3–5). Similar treatment of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranosides (**10**) showed

Table 2
Reductive cleavage of *O*-benzylidene acetals by DIBAL-H[a]

Entry		DIBAL-H solution (mol equiv)	Solvent (M)	Temperature (°C)	Time (h)	Products (yield/%)[b]			
1	 **4**	CH_2Cl_2 (3.0)	—	0	1.5	 **5**	0	 **6**	89
2		Toluene (3.0)	Toluene (0.2)	−10	15.0		69		13
3	 **7**	CH_2Cl_2 (3.0)	—	0	3.0	 **8**	0	 **9**	83
4		CH_2Cl_2 (3.0)	—	0	0.5		0		91
5		Toluene (3.0)	Toluene (0.2)	−10	3.0		0		86
						 **11**		 **12**	
6	 ***exo*-10**	CH_2Cl_2 (2.2)	CH_2Cl_2 (0.2)	0	0.3		75		19
7		Toluene (2.2)	Toluene (0.2)	−40 to 0	4.0[c]		3		92
8[d]		Toluene (2.2)	Toluene (0.2)	0	1.0		84		15
9	 ***endo*-10**	CH_2Cl_2 (2.2)	CH_2Cl_2 (0.2)	−40 to 0	2.5[e]		76		3
10		Toluene (2.2)	Toluene (0.2)	−40 to 0	4.0[c]		91		6
11[d]		Toluene (2.2)	Toluene (0.2)	0	1.0		96		2
12	**10**[f]	CH_2Cl_2 (2.2)	CH_2Cl_2 (0.2)	−40 to 0	2.5[e]		61		26
13[d]		Toluene (2.2)	Toluene (0.2)	0	1.0		82		7

[a] Reactions were performed by DIBAL-H (1.1 mL (2.2 equiv) or 1.5 mL (3.0 equiv); 1 M solution in CH_2Cl_2 or toluene) with benzylidene acetals (0.5 mmol; 1 M solution in toluene or CH_2Cl_2, or solvent free).
[b] After isolation by column chromatography on silica gel.
[c] Reaction was performed at −40 °C for 1 h, and then at 0 °C for 3 h.
[d] Reaction was performed in the presence of $AlCl_3$ (5 mol %).
[e] Reaction was performed at −40 °C for 1 h, and then at 0 °C for 1.5 h.
[f] A mixture of *exo*-**10** and *endo*-**10** (1:1).

that reductive opening of the 2,3-*O*-benzylidene acetal was faster than opening of the 4,6-*O*-benzylidene acetal. The regioselectivity of ring opening of this 2,3-*O*-benzylidene acetal depended on the solvent of the stock solution of DIBAL-H in the case of *exo*-**10** (entries 6–8), where the use of dichloromethane and toluene gave the 2-*O*-benzyl derivative **11** and 3-*O*-benzyl derivative **12** as major products, respectively. Similar solvent dependence was not observed in the case of *endo*-**10** (entries 9–11).

On the other hand, Hung and co-workers showed that *p*-tolyl 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside was prepared in 70% from the corresponding trimethylsilylated mannoside derivative, as stated in the 'Supplementary data' of their report.[2] It is also reported that *exo*-**10** gave **12** selectively by LAH (4.75 equiv) in the presence of $AlCl_3$ (4.06 equiv) in 56% yield,[6b–d] although *endo*-**10** gave **11** selectively by DIBAL-H (2.2 equiv) in toluene at −40 °C for 21 h in 85% (with 10% of **12**),[6a] and LAH (4.75 equiv) in the presence of $AlCl_3$ (4.06 equiv) in refluxing dichloromethane–ether co-solvent for 10 min also gave **11** selectively in 46% yield.[6b] Therefore, we believe that this is the most convenient method for obtaining methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannoside (**12**) from mannose, since *exo*-**10** is more easily available rather than *endo*-**10**.

Reductive ring-opening reaction of 1,2-*O*-benzylidene-α-D-glucopyranose using DIBAL-H has been reported by Yamaura and co-workers.[5] However, they and we have not examined the possible solvent effect of the stock solution of DIBAL-H, although they clearly described no difference in the reaction when using either toluene or dichloromethane as solvent.

Various metal hydride reducing reagents in the presence of Lewis acid have been used for the ring opening of benzylidene acetals of hexopyranoside derivatives to give *O*-benzyl-protected hexopyranoside derivatives as shown in Scheme 1. We discovered that 3 (or 2.2) equiv of a dichloromethane or a toluene solution of DIBAL-H can serve as an effective reductant without a Lewis acid to give the corresponding 4- or 6-*O*-benzyl-protected hexopyranoside derivative highly regioselectively. Moreover, we have shown that the regioselectivity of ring opening with DIBAL-H depends on the solvent employed, specifically dichloromethane or toluene, although the exact reason for this selectivity is not yet clear. Since the selectivity slightly depends to some extent on the age of the reducing reagent, we would like to propose that information on the age of the reagent be included in reports describing the use of solutions of DIBAL-H alongside the reaction conditions and the reaction solvents employed.

1. Experimental

1.1. General methods

Substances **1**, **4**, **7**, and **10** were prepared according to known procedures[7] and their modified procedures as shown in the

Supplementary data (see electronic version for this information). Commercially available dry solvents purchased from Wako Pure Chemical Industries, Ltd were used without further purification.

1.2. General procedure for reductive cleavage of 4,6-*O*-benzylidene acetals using a toluene solution of DIBAL-H

To a solution of 4,6-*O*-benzylidenepyranoside (0.5 mmol) in toluene (0.2 M) was added diisobutylaluminum hydride (1 M of toluene solution of DIBAL-H, 1.5 mL; 1.5 mmol) dropwise at −10 °C under a nitrogen atmosphere, and the reaction mixture was stirred for 15 h. After the reaction mixture was quenched by the addition of methanol at −10 °C, aq KOH (10%) was added to the mixture at room temperature. The mixture was extracted with Et_2O. The extract was dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by chromatography on silica gel to give the corresponding alcohols.

1.3. General procedure for reductive cleavage of 4,6-*O*-benzylidene acetals using a dichloromethane solution of DIBAL-H

To 4,6-*O*-benzylidenepyranoside (0.5 mmol) was added diisobutylaluminum hydride (1.5 mL, 1.5 mmol) in dichloromethane (1 M) dropwise at 0 °C with stirring, and the reaction mixture was stirred for 1.5 h. The reaction mixture was diluted by chloroform, and the reaction mixture was quenched by addition of methanol at 0 °C. To the reaction mixture was added 10% aq KOH at room temperature, and the mixture was extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and concentrated in vacuo. The product was isolated by chromatography on silica gel.

1.4. Preparation of methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (2)

Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) was reduced by a toluene solution of DIBAL-H to give methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**2**, 211.3 mg, 91.1% yield): white solid; R_f 0.24 (2:1 hexane–EtOAc); $[\alpha]_D^{25}$ 24.2 (*c* 1.00, $CHCl_3$) (lit.[3h] $[\alpha]_D$ 20 (*c* 1.25, $CHCl_3$)); mp 65–67 °C; IR ($CHCl_3$) 3481, 3031, 2925, 2361, 1497, 1454, 1361, 1071, 911, 738, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.61 (br s, 1H, OH), 3.37 (s, 3H), 3.48–3.54 (m, 2H), 3.63–3.79 (m, 3H), 4.01 (t, J = 9.2 Hz, 1H), 4.57 (d, J = 3.6 Hz, 1H; anomeric), 4.66, 4.80 (each AB, J_{AB} = 12.0 Hz, each 1H), 4.64, 4.88 (each AB, J_{AB} = 11.2 Hz, each 1H), 4.84, 4.99 (each AB, J_{AB} = 10.8 Hz, each 1H), 7.27–7.37 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 61.9, 70.7, 73.4, 75.0, 75.7, 77.4, 80.0, 81.9, 98.1, 127.5–128.4 (15 × CH-aromatic), 138.0, 138.1, 138.7; HRFABMS: *m/z* calcd for $C_{28}H_{32}O_6$ $[M]^+$ 464.2199; found 464.2170.

1.5. Preparation of methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (3)

Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) was reduced by a dichloromethane solution of DIBAL-H to give methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (**3**, 190.7 mg, 82.1% yield): colorless oil; R_f 0.42 (2:1 hexane–EtOAc); $[\alpha]_D^{25}$ 21.4 (*c* 1.00, $CHCl_3$) (lit.[3h] $[\alpha]_D$ 9 (*c* 1.22, $CHCl_3$)); IR (neat) 3493, 3402, 2936, 2361, 1728, 1496, 1451, 1069, 918, 859, 739, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.33 (br d, J = 2.8 Hz, 1H, OH), 3.40 (3H, s), 3.55 (dd, J = 9.6, 3.6 Hz, 1H), 3.62 (ddd, J = 9.3, 9.3, 2.0 Hz, 1H), 3.68–3.74 (m, 3H), 3.8 (t, J = 9.0 Hz, 1H), 4.55, 4.60 (each AB, J_{AB} = 11.6 Hz, each 1H), 4.65 (d, J = 3.6 Hz, 1H, anomeric), 4.67, 4.78 (each AB, J_{AB} = 12.2 Hz, each 1H), 4.75, 5.01 (each AB, J_{AB} = 11.2 Hz, each 1H), 7.27–7.38 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.0, 69.3, 69.8, 70.5, 72.8, 73.3, 75.1, 79.4, 81.2, 97.9, 127.3–128.2 (15 × CH-aromatic), 137.7, 137.8, 138.5; HRFABMS: *m/z* calcd for $C_{28}H_{32}O_6$ $[M]^+$ 464.2199, found 464.2217.

1.6. Preparation of methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (5)

Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside **4** was reduced by a toluene solution of DIBAL-H to give methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside (**5**, 160.8 mg, 69.3% yield): colorless oil; R_f 0.22 (2:1 hexane–EtOAc); $[\alpha]_D^{25}$ 36.0 (*c* 0.10, $CHCl_3$) (lit.[3e] $[\alpha]_D^{29}$ −5.56 (*c* 1.2, $CHCl_3$)); IR (neat) 3473, 3031, 2936, 2361, 1718, 1701, 1497, 1454, 1354, 1195, 1097, 1050, 913, 829, 742, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.76 (br s, 1H), 3.30 (s, 3H), 3.60–3.64 (m, 1H), 3.75–3.99 (m, 5H), 4.63 (s, 2H), 4.70 (d, J = 2.4 Hz, 1H), 4.69, 4.78 (each ABq, J_{AB} = 12.4 Hz, each 1H), 4.65, 4.94 (each AB, J_{AB} = 11.2 Hz, each 1H), 7.27–7.37 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.6, 62.1, 72.1, 72.1, 72.8, 74.7, 74.7, 75.0, 80.0, 99.1, 127.3–128.1 (15 × CH-aromatic), 138.0, 138.3, 138.3; HRFABMS: *m/z* calcd for $C_{28}H_{32}O_6$ $[M]^+$ 464.2199, found 464.2170.

1.7. Preparation of methyl 2,3,6-tri-*O*-benzyl-α-D-mannopyranoside (6)

Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**4**) was reduced by a dichloromethane solution of DIBAL-H to give methyl 2,3,6-tri-*O*-benzyl-α-D-mannopyranoside (**6**, 206.5 mg, 89.0% yield): colorless oil; R_f 0.40 (2:1 hexane–EtOAc); $[\alpha]_D^{25}$ −2.0 (*c* 0.20, $CHCl_3$); IR (neat) 3447, 3030, 2914, 2361, 1497, 1454, 1363, 1206, 1060, 967, 908, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.49 (br d, 1H), 3.35 (s, 3H), 3.68–3.82 (m, 5H), 4.04 (ddd, J = 9.5, 9.5, 1.6 Hz, 1H), 4.50 and 4.59 (each AB, J_{AB} = 11.6 Hz, 1H and 1H), 4.59, 4.64 (each AB, J_{AB} = 12.0 Hz, each 1H), 4.65, 4.70 (each AB, J_{AB} = 12.0 Hz, each 1H), 4.78 (d, J = 1.2 Hz, 1H; anomeric), 7.26–7.36 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.8, 67.8, 70.4, 71.4, 71.7, 72.6, 73.5, 73.9, 79.6, 99.1, 127.4–128.3 (15 × CH-aromatic), 138.1, 138.1, 138.2; HRFABMS: *m/z* calcd for $C_{28}H_{32}O_6$ $[M]^+$ 464.2199, found 464.2176.

1.8. Preparation of methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (9)

Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside (**7**) was reduced by a toluene solution of DIBAL-H to give methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (**9**, 199.9 mg, 86.2% yield). Methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-galactopyranoside (**7**) was reduced by a dichloromethane solution of DIBAL-H to give methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (**9**, 210.3 mg, 90.7% yield): colorless oil; R_f 0.56 (10:1 $CHCl_3$–EtOAc); $[\alpha]_D^{25}$ 38.0 (*c* 0.20, $CHCl_3$) (lit.[3h] $[\alpha]_D$ 37 (*c* 1.0, $CHCl_3$)); IR (neat) 3448, 1631, 1456, 1349, 1277, 1205, 1092, 1036, 750, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 1H), 3.38 (s, 3H), 3.65–3.75 (m, 2H), 3.86–3.91 (m, 3H), 4.06 (s, 1H), 4.55, 4.59 (each AB, J_{AB} = 11.6 Hz, each 1H), 4.68 (s, 1H), 4.71, 4.79 (each AB, J_{AB} = 11.8 Hz, each 1H), 4.66, 4.81 (each AB, J_{AB} = 12.0 Hz, each 1H), 7.26–7.36 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 68.1, 68.4, 69.6, 72.8, 73.5, 73.6, 75.7, 77.6, 98.6, 127.6–128.4 (15 × CH-aromatic), 137.9, 138.1, 138.3; HRFABMS: *m/z* calcd for $C_{28}H_{32}O_6$ $[M]^+$ 464.2199, found 464.2188.

1.9. Preparation of methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (11)

To a stirred suspension of methyl *endo*-2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside (*endo*-**10**, 185.1 mg, 0.5 mmol) in

toluene (2.5 mL) was added a toluene solution of DIBAL-H (1.1 mL, 1.1 mmol) dropwise at −40 °C, and the mixture was stirred for 1 h at −40 °C and then for 3 h at 0 °C. The reaction mixture was quenched by the addition of MeOH (1 mL) at 0 °C, and then aq KOH (10%) was added to the mixture. The reaction mixture was extracted twice with ether, and the combined extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**11**, 168.9 mg, 90.8% yield): colorless solid; R_f 0.52 (2:1 hexane–EtOAc); mp 43–45 °C (lit.[6a] 44–46 °C); $[\alpha]_D^{25}$ 2.80 (*c* 0.50, $CHCl_3$) (lit.[6a] $[\alpha]_D^{24}$ 1.1 (*c* 1.0, $CHCl_3$)); IR ($CHCl_3$) 3481, 3033, 2910, 1958, 1887, 1815, 1719, 1605, 1496, 1454, 1382, 1315, 1281, 1211, 1101, 971, 912, 878, 800, 751, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (d, J = 8.0 Hz, 1H; OH), 3.37 (s, 3H), 3.74–3.86 (m, 3H), 3.91 (t, J = 9.2 Hz, 1H), 4.05–4.10 (m, 1H), 4.26 (dd, J = 9.6, 4.0 Hz, 1H), 4.69, 4.76 (each AB, J_{AB} = 11.6 Hz, each 1H), 4.75 (d, J = 1.6 Hz, 1H; anomeric), 5.58 (s, 1H), 7.32–7.38 (m, 8H), 7.48–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.0, 63.3, 68.7, 68.8, 73.7, 78.5, 79.5, 99.4, 102.1, 126.2–129.0 (10 × CH-aromatic), 137.3, 137.5; HRFABMS: *m/z* calcd for $C_{21}H_{25}O_6$ $[M+H]^+$ 373.1651, found 373.1643.

1.10. Preparation of methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (12)

To a stirred solution of methyl *exo*-2,3;4,6-di-*O*-benzylidene-α-D-mannopyranoside (*exo*-**10**, 185.1 mg, 0.5 mmol) in toluene (2.5 mL) was added a toluene solution (1 M) of DIBAL-H (1.1 mL, 1.1 mmol) dropwise at −40 °C, and the mixture was stirred for 1 h, and then stirred for 3 h at 0 °C. The reaction mixture was quenched by the addition of MeOH at −0 °C, and then 10% aq KOH was added to the mixture at room temperature. The reaction mixture was extracted with Et_2O, and the extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (**12**, 177.8 mg, 95.5% yield): colorless oil; R_f 0.31 (2:1 hexane–EtOAc); $[\alpha]_D^{25}$ 54.0 (*c* 0.50, $CHCl_3$) (lit.[8] $[\alpha]_D$ 47 (*c* 1.1, $CHCl_3$)); IR ($CHCl_3$) 3467, 3033, 2911, 1956, 1887, 1813, 1734, 1605, 1496, 1454, 1375, 1320, 1214, 1099, 977, 914, 876, 797, 750, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.65 (br d, J = 1.2 Hz, 1H, OH), 3.38 (s, 3H), 3.78–3.92 (m, 3H), 4.05–4.12 (m, 2H), 4.28 (dd, J = 9.4, 3.8 Hz, 1H), 4.77 (d, J = 1.6, 1H, anomeric), 4.72, 4.86 (each AB, J_{AB} = 11.8 Hz, each 1H), 5.62 (s, 1H), 7.29–7.41 (m, 8H), 7.48–7.51 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.9, 63.1, 68.8, 69.8, 72.9, 75.5, 78.7, 100.9, 101.5, 125.9–128.8 (10 × CH-aromatic), 137.4, 137.8; HRFABMS: *m/z* calcd for $C_{21}H_{25}O_6$ $[M+H]^+$ 373.1651, found 373.1643.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2008.07.017.

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