Glycosidation with 1-Hydroxy Sugars as Glycosyl Donors Promoted by Trimethylsilyl Chloride and Zinc Triflate

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1-Hydroxy sugars (1a—4a) were directly coupled with free alcohols (5b—d) to give the corresponding glycosides by using trimethylsilyl chloride and zinc triflate as promoters.

Keywords glycosidation; 1-hydroxy sugar; trimethylsilyl chloride; zinc triflate

The glycosidation reaction is one of the most important in carbohydrate chemistry.[1] In previous papers,[2] a new glycosidation method using stable glycosyl esters as glycosyl donors promoted by trimethylsilyl chloride (TMSCl) and zinc triflate ($Zn(OTf)_2$), was reported. Some glycosidations using 1-hydroxy sugars as glycosyl donors were also reported.[3] In this paper, the author applied the method to benzyl-protected 1-hydroxy sugars (**1a—4a**) to extend the utility of this glycosidation method.

Results and Discussion

The 1-hydroxy sugars (**1a—4a**) used here as glycosyl donors and the alcohols (**5b—d**) used as glycosyl acceptors are shown in Chart 1. The reaction of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1a**) ($\alpha/\beta=87/13$) with 8-methoxycarbonyloctanol (**5b**) (2 eq)[4] in dichloromethane in the presence of a mixture of TMSCl (1.5 eq) and $Zn(OTf)_2$ (0.3 eq) gave the corresponding glycoside (**1b**) ($\alpha/\beta=80/20$) in 79% yield (Table I, run 1).

Solvent effect was investigated in the reaction of **1a** and **5b** in the presence of a mixture of TMSCl and $Zn(OTf)_2$ as promoters. The results (runs 1—3) clearly showed that acetonitrile (run 2) was the solvent of choice in terms of yield. When TMSCl (1.5 eq) and $Zn(OTf)_2$ (1.5 eq) were used, the yield decreased to 74% ($\alpha/\beta=82/18$) (run 4). Also, when **1a** and **5b** were allowed to reacted in acetonitrile in the presence of trimethylsilyl triflate (TMSOTf) (0.3 eq for run 5 or 1.5 eq for run 6)[5] instead of TMSCl and $Zn(OTf)_2$ as a promoter for 4 h, **1b** was obtained in 53% ($\alpha/\beta=43/57$) and 67% ($\alpha/\beta=84/16$) yields, respectively. These results showed that the combination of TMSCl and $Zn(OTf)_2$ was more reactive than TMSOTf.

In a similar manner, the reaction of 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranose (**2a**), 2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (**3a**) ($\alpha/\beta=60/40$) and 2,3,4-tri-*O*-benzyl-L-fucopyranose (**4a**) ($\alpha/\beta=96/4$)[6] with **5b** in the presence of TMSCl and $Zn(OTf)_2$ gave **2b**, **3b** and **4b**, respectively (runs 7—9). Next, the reactions of **1a—4a** with β-cholestanol (**5c**) were investigated. Since **5c** showed poor

TABLE I. Glycosidation with 1-Hydroxy Sugars[a]

Run	Donor	Acceptor	Solvent	Time (h)	Yield[b] (%)	$\alpha:\beta$[c]
1	**1a**	**5b**	CH_2Cl_2	4	79	80:20
2	**1a**	**5b**	MeCN	4	97	64:36
3	**1a**	**5b**	$PhCH_3$	4	73	68:32
4	**1a**	**5b**	MeCN[d]	4	74	82:18
5	**1a**	**5b**	MeCN[e]	4	53	43:57
6	**1a**	**5b**	MeCN[f]	4	67	84:16
7	**2a**	**5b**	MeCN	4	89	98: 2
8	**3a**	**5b**	MeCN	4	93	65:35
9	**4a**	**5b**	MeCN	4	92	61:39
10	**1a**	**5c**	CH_2Cl_2	5	63	49:51
11	**2a**	**5c**	CH_2Cl_2	4	43	88:12
12	**3a**	**5c**	CH_2Cl_2	3	61	62:38
13	**4a**	**5c**	CH_2Cl_2	2.5	95	73:27
14	**1a**	**5d**	MeCN	1	76	55:45

a) All reactions were carried out at room temperature. The ratio of donor: acceptor: TMSCl: $Zn(OTf)_2$ was 1.0:2.0:1.5:0.3 except in runs 4—6. *b*) Isolated total yield. *c*) The $\alpha:\beta$ ratios were determined by ^{1}H-NMR analysis. *d*) The ratio of donor: acceptor: TMSCl: $Zn(OTf)_2$ was 1.0:2.0:1.5:1.5. *e*) The ratio of donor: acceptor: TMSOTf was 1.0:2.0:0.3. *f*) The ratio of donor: acceptor: TMSOTf was 1.0:2.0:1.5.

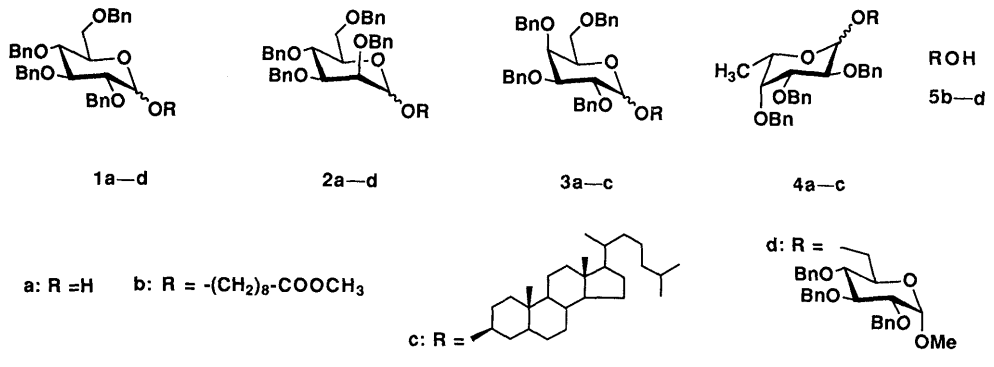

Chart 1

solubility in acetonitrile, the reactions were carried out in dichloromethane. All the reactions resulted in the formation of the corresponding glycosides (**1c—4c**) (runs 10—13). The reaction of **1a** with a glycosyl alcohol (**5d**) gave the disaccharide (**1d**) ($\alpha/\beta = 55/45$) in 76% yield (run 14).

In summary, the combination of TMSCl and $Zn(OTf)_2$ can serve as an efficient promoter of glycosidation with 1-hydroxy sugars as glycosyl donors.

Experimental

Optical rotations were measured in chloroform with a Perkin-Elmer 241 polarimeter. ^{1}H-NMR spectra were obtained on a Varian VXR-500 spectrometer (500 MHz) in deuteriochloroform using tetramethylsilane as internal standard. IR spectra were obtained on a Hitachi 270-30 infrared spectrophotometer. MS and HRMS were obtained on a JEOL JMS-HX110 mass spectrometer. Column chromatography was performed with Merck Silica gel 60 (230—430 mesh). Glycosyl donors **1a**—**3a** were purchased from Sigma Chemical Co., Ltd. The glycosyl acceptor **5d** was purchased from Junsei Chemical Co., Ltd.

Typical Procedure for the Glycosidation TMSCl (0.038 ml, 0.3 mmol) was added in one portion to a mixture of 1-hydroxy sugar (0.2 mmol), alcohol (0.4 mmol) and $Zn(OTf)_2$ (22 mg, 0.06 mmol) in a solvent (3 ml) at room temperature, and the mixture was stirred for the period shown in Table I. The reaction mixture was directly chromatographed on silica gel (50 g) with toluene–ethyl acetate (19 : 1) to give an epimeric glycoside mixture. Analytical samples were prepared by repeated silica gel column chromatography.

Glycosidation Using Trimethylsilyl Triflate (Table I, Runs 5 and 6) TMSOTf (0.012 ml, 0.06 mmol for run 6 or 0.058 ml, 0.3 mmol for run 5) was added to a mixture of 1-hydroxy sugar **1a** (108 mg, 0.2 mmol) and alcohol **5b** (76 mg, 0.4 mmol) in acetonitrile (3 ml) at room temperature, and the mixture was stirred for 4 h. The reaction mixture was directly chromatographed on silica gel (50 g) with toluene–ethyl acetate (19 : 1) to give an epimeric mixture of **1bα** and **1bβ** as a colorless oil.

Spectral data for glycosides **1c**,[2a] **1d**,[7] **2b**, **c**,[2b] **3c**,[2a] **4b**,[8] and **4c**[2a] were identical with reported values.

1bα: a colorless oil. $[\alpha]_D$ +37.4° (c = 1.09). ^{1}H-NMR δ: 1.26—1.35 (8H, m), 1.57—1.63 (4H, m), 2.29 (2H, t, J = 7.6 Hz, C$\underline{H}_2$–COOCH$_3$), 3.41 (1H, dt, J = 9.8, 6.8 Hz, CH$_2$–O), 3.15 (1H, dd, J = 3.4, 9.8 Hz, H-2), 3.59—3.65 (3H, m, H-4, 5, CH$_2$–O), 3.66 (3H, s, OCH$_3$), 3.72 (1H, dd, J = 3.7, 10.5 Hz, H-6), 3.77 (1H, dd, J = 1.7, 10.5 Hz, H-6), 3.98 (1H, dd, J = 9.0, 9.8 Hz, H-3), 4.47 (1H, d, J = 11.5 Hz, ArCH$_2$), 4.47 (1H, d, J = 11.0 Hz, ArCH$_2$), 4.60 (1H, d, J = 11.5 Hz, ArCH$_2$), 4.64 (1H, d, J = 12.2 Hz, ArCH$_2$), 4.75 (1H, d, J = 3.4 Hz, H-1), 4.77 (1H, d, J = 12.2 Hz, ArCH$_2$), 4.81 (1H, d, J = 10.7 Hz, ArCH$_2$), 4.82 (1H, d, J = 10.7 Hz, ArCH$_2$), 4.99 (1H, d, J = 11.0 Hz, ArCH$_2$), 7.12—7.14 (2H, m, ArH), 7.22—7.36 (18H, m, ArH). IR (KBr): 2932, 2864, 1738, 1498, 1456, 1362 cm^{-1}. MS m/z: 710 (M$^+$), 619 (M$^+$ − C$_7$H$_7$). HRMS Calcd for C$_{44}$H$_{54}$O$_8$–C$_7$H$_7$ 619.3271. Found: 619.3257.

1bβ: a colorless oil. $[\alpha]_D$ +5.37° (c = 2.46). ^{1}H-NMR δ: 1.28—1.41 (8H, m), 1.54—1.67 (4H, m), 2.28 (2H, t, J = 7.8 Hz, C$\underline{H}_2$–COOCH$_3$), 3.44 (1H, dd, J = 7.8, 9.0 Hz, H-2), 3.45 (1H, ddd, J = 2.0, 4.9, 9.0 Hz, H-5), 3.52 (1H, dt, J = 9.8, 7.1 Hz, CH$_2$–O), 3.57 (1H, dd, J = 9.0, 9.5 Hz, H-3), 3.64 (1H, dd, J = 9.0, 9.5 Hz, H-4), 3.66 (3H, s, OCH$_3$), 3.67 (1H, dd, J = 4.9, 10.1 Hz, H-6), 3.74 (1H, dd, J = 2.0, 10.1 Hz, H-6), 3.95 (1H, dt, J = 9.8, 6.6 Hz, CH$_2$–O), 4.38 (1H, d, J = 7.8 Hz, H-1), 4.52 (1H, d, J = 11.0 Hz, ArCH$_2$), 4.55 (1H, d, J = 12.2 Hz, ArCH$_2$), 4.61 (1H, d, J = 12.2 Hz, ArCH$_2$), 4.71 (1H, d, J = 11.0 Hz, ArCH$_2$), 4.78 (1H, d, J = 11.0 Hz, ArCH$_2$), 4.81 (1H, d, J = 11.2 Hz, ArCH$_2$), 4.92 (1H, d, J = 11.0 Hz, ArCH$_2$), 4.95 (1H, d, J = 11.2 Hz, ArCH$_2$), 7.14—7.16 (2H, m, ArH), 7.24—7.36 (18H, m, ArH). IR (KBr): 2932, 2860, 1738, 1498, 1456, 1364 cm^{-1}. MS m/z: 710 (M$^+$), 619 (M$^+$ − C$_7$H$_7$). HRMS Calcd for C$_{44}$H$_{54}$O$_8$–C$_7$H$_7$ 619.3271. Found: 619.3250.

3bα: a colorless oil. $[\alpha]_D$ +25.1° (c = 1.06). ^{1}H-NMR δ: 1.26—1.32 (8H, m), 1.51—1.62 (4H, m), 2.28 (2H, t, J = 7.6 Hz, C$\underline{H}_2$-COOCH$_3$), 3.41 (1H, dt, J = 9.8, 6.6 Hz, CH$_2$–O), 3.52 (2H, m, H-3, 5), 3.61 (1H, dt, J = 9.8, 7.1 Hz, CH$_2$–O), 3.66 (3H, s, OCH$_3$), 3.93—3.97 (3H, m, H-4, 6), 4.02 (1H, dd, J = 3.7, 6.3 Hz, H-2), 4.39 (1H, d, J = 12.0 Hz, ArCH$_2$), 4.47 (1H, d, J = 12.0 Hz, ArCH$_2$), 4.57 (1H, d, J = 11.5 Hz, ArCH$_2$), 4.66 (1H, d, J = 12.0 Hz, ArCH$_2$), 4.73 (1H, d, J = 11.5 Hz, ArCH$_2$), 4.81 (1H, d, J = 3.7 Hz, H-1), 4.81 (1H, d, J = 12.0 Hz, ArCH$_2$), 4.85 (1H, d, J = 11.5 Hz, ArCH$_2$), 4.94 (1H, d, J = 11.5 Hz, ArCH$_2$), 7.23—7.39 (20H, m, ArH). IR (KBr): 2932, 2864, 1738, 1498, 1456, 1348 cm^{-1}. MS m/z: 710 (M$^+$), 619 (M$^+$ − C$_7$H$_7$). HRMS Calcd for C$_{44}$H$_{54}$O$_8$–C$_7$H$_7$ 619.3271. Found: 619.3285.

3bβ: a colorless oil. $[\alpha]_D$ +0.79° (c = 1.01). ^{1}H-NMR δ: 1.27—1.54 (8H, m), 1.56—1.64 (4H, m), 2.28 (2H, t, J = 7.6 Hz, C$\underline{H}_2$–COOCH$_3$), 3.47 (1H, dt, J = 9.5, 7.1 Hz, CH$_2$–O), 3.48—3.53 (2H, m, H-3, 5), 3.58 (2H, d, J = 6.4 Hz, H-6), 3.66 (3H, s, OCH$_3$), 3.81 (1H, dd, J = 7.6, 9.8 Hz, H-2), 3.88 (1H, d, J = 5.0 Hz, H-4), 3.91 (1H, dt, J = 9.5, 6.8 Hz, CH$_2$–O), 4.33 (1H, d, J = 7.6 Hz, H-1), 4.41 (1H, d, J = 12.0 Hz, ArCH$_2$), 4.45 (1H, d, J = 12.0 Hz, ArCH$_2$), 4.61 (1H, d, J = 11.7 Hz, ArCH$_2$), 4.70 (1H, d, J = 12.0 Hz, ArCH$_2$), 4.73 (1H, d, J = 12.0 Hz, ArCH$_2$), 4.75 (1H, d, J = 11.5 Hz, ArCH$_2$), 4.92 (1H, d, J = 11.5 Hz, ArCH$_2$), 4.93 (1H, d, J = 11.7 Hz, ArCH$_2$), 7.23—7.36 (20H, m, ArH). IR (KBr): 2936, 2864, 1738, 1498, 1456, 1366 cm^{-1}. MS m/z: 710 (M$^+$), 619 (M$^+$ − C$_7$H$_7$). HRMS Calcd for C$_{44}$H$_{54}$O$_8$–C$_7$H$_7$ 619.3271. Found: 619.3286.

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