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A Facile Glycosylation of Spirostanol Catalyzed by Cadmium Carbonate

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Abstract: A facile glycosylation for the synthesis of spirostanol glycosides was reported. Using cadmium carbonate as a catalyst in CH_3CN, a series of saponins was synthesized efficiently in a satisfactory yield.

Keywords: Spirostanol glycosides, glycosylation, cadmium carbonate.

Spirostanol glycosides are a large group of steroidal saponins. They are existent in nature extensively and have a broad range of interesting bioactivities[1]. The sugar moiety of spirostanol saponins usually links at position 3 of the spirostan aglycone. Many kinds of glycosylation methods have been used in the synthesis of these saponins[2].

Cadmium carbonate, a commercially available cheap reagent, had been used as the catalyst to synthesize steroidal aryl glucuronides and/or glucosides[3]. In order to synthesize the bioactive spirostanol glycosides, cadmium carbonate was used as promoter to catalyze the coupling of sapogenins with a series of acetobromosugars in non-protic solvents such as acetonitrile, methylene chloride, toluene and so on. Acetonitrile was a preferred solvent for better yield. Using this method, formation of the corresponding orthoester, which often occurred in coupling acetosugar trichloroacetimidate with spirostanol, could be avoided[2c].

In our work, some typical acetobromomono- or disaccharides were used as donors to glycosylate three sapogenins: diosgenin **1**, hecogenin **2** and 11-ketotigogenin **3**. The results were shown in **Table 1**. For example, peracetylated disaccharide α-bromide ("acetobromocellobiose", "acetobromolactose", and 2,4,6,-tri-*O*-acetyl-3-*O*-(2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl)-α-D-glucopyranosyl bromide[4]) was coupled with these three spirostanols, the corresponding spirostanol β-*O*-disaccharide peracetates were obtained in 83-89% yield and no α-isomer was detected. When acetobromoglucose was used as donor, there was a little α-isomer along with the bulk of spirostanol β-O-glucoside tetraacetate in ratio of α/β-isomers about 1/15 and the total yield was 90-92%. The C2 acetate was replaced by perbenzoyl rhamnosyl in donor 3,4,6-tri-*O*-acetyl-2-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl)-α-D-glucopyranosyl bromide[5], the amount of spirostanol α-O-disaccharide became more sizable (the ratio of

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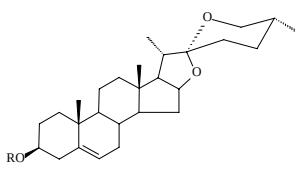
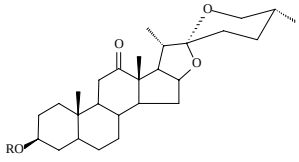
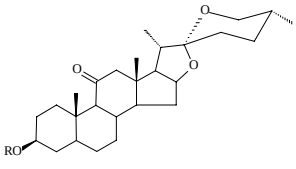


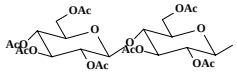
1. R=H
1a. R=X_1 **1e**. R=X_5
1b. R=X_2 **1f**. R=X_6
1c. R=X_3 **1g**. R=X_7
1d. R=X_4 **1h**. R=X_8



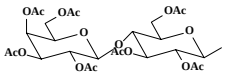
2. R=H
2a. R=X_1
2b. R=X_2
2c. R=X_3
2d. R=X_4



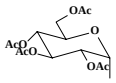
3. R=H
3a. R=X_1
3b. R=X_2



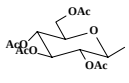
X_1



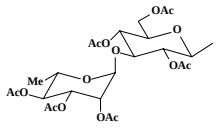
X_2



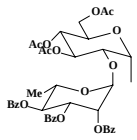
X_3



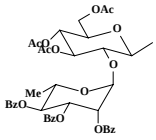
X_4



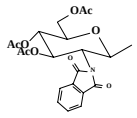
X_5



X_6



X_7



X_8

α/β-isomers was about 1/7), because of the loss of acetyl neighboring group participation effect. In our reaction condition, trace amount of by-products: 3-*O*-acetyl diosgenin, 3-*O*-acetyl hecogenin was detected. These by-products were formed by acetyl transfer from sugar donors.

Myszka used AgOTf as promoter to couple N-tetrachlorophthaloyl-protected bromide of D-glucosamine with diosgenin in an acceptable yield[6]. With our glycosylation procedure, diosgenyl 2-deoxy-2-phthalimido-3, 4 ,6-tri-*O*-acetyl-β-D-glucopyranoside was obtained in a yield of 82%.

Deprotection of the above products with NaOMe (for **1h**, then the second deprotection step with H_2NNH_2-H_2O) could get corresponding spirostanol mono- or disaccharides.

This facile glycosylation was suitable for the preparation of spirostanol glycosides in large scale. Compound **1a, 2a, 3a** used to be prepared in batches up to 60 g.

General procedure for glucosylation

The optimized operating condition:1 eq. of sapogenin, 2.5 eq. of $CdCO_3$ were added into acetonitrile (anh.), and refluxed with partial removal of solvent in order to keep the reaction system anhydrous. At room temperature, 2.5 eq. of sugar donor was added into the flask. The mixture was refluxed under Ar for 2 hours, then diluted with CH_2Cl_2, filtered through celite and concentrated under vacuum. Chromatography of the residue on a silica gel column (petroleum ether:acetone 8:1→4:1) afforded the corresponding protected spirostan saponins.

Table 1 Glycosylation of spirostanol with $CdCO_3$ as a promoter in CH_3CN

Spirostanol	Sugar donor	Product	^{1}H NMR data of anomeric H[d] δ ppm	J Hz	α-/β-Isomer	Yield (%)
1	acetobromocellobiose	**1a**	1′-H, 4.54, d, 8.1			89
			1″-H, 4.49, d, 7.8			
2	acetobromocellobiose	**2a**	1′-H, 4.52, d, 8.1			88
			1″-H, 4.48, d, 8.1			
3	acetobromocellobiose	**3a**	1′-H, 4.52, d, 8.1			83
			1″-H, 4.48, d, 8.1			
1	acetobromolactose	**1b**	1′-H, 4.55, d, 8.4			86
			1″-H, 4.47, d, 7.8			
2	acetobromolactose	**2b**	1′-H, 4.53, d, 7.8			84
			1″-H, 4.46, d, 7.8			
3	acetobromolactose	**3b**	1′-H, 4.54, d, 7.8			86
			1″-H, 4.47, d, 7.8			
1	acetobromoglucose	**1c & 1d**	**1c**, 1′-H, 4.54, d, 8.1		1/15	92
			1d, 1″-H, 4.49, d, 7.8			
2	acetobromoglucose	**2c & 2d**	**2c**, 1′-H, 4.54, d, 8.1		1/15	90
			2d, 1″-H, 4.49, d, 7.8			
1	Donor A[a]	**1e**	*See note 7*		/	83
1	Donor B[b]	**1f & 1g**	*See note 7*		1/7	78
1	Donor C[c]	**1h**	*See note 7*		/	82

a: 2,4,6-Tri-O-acetyl-3-O-(2,3,4-tri-O-acetyl-α-L-rhamnopyranosyl)-α-D-glucopyranosyl bromide[4].

b: 3,4,6-Tri-O-acetyl-2-O-(2,3,4-tri-O-benzoyl-α-L-rhamnopyranosyl)-α-D-glucopyranosyl bromide[5].

c: 3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido-α,β-D-glucopyranosyl bromide[6].

d: 300MHz in $CDCl_3$.

Rerferences and Notes

1. (a) S. B. Mahato, A. N. Ganguly, N. P. Sahu, *Phytochemistry*, **1982**, *21*, 959. (b) K. Hosettmann, A, Marson, *Saponins*, Camdrige University Press: New York, **1995**.
2. (a) M. R. Mailinow, J. O. Gardner, J. T. Nelson, P. Mclaughlin, B. Upson, R. Aigner-Heid, *Steroids*, **1986**, *48*, 197. (b) G. Wulff, G, Röhle, *Angew. Chem. Int. Ed. Engl*., **1974**, *13*, 157 (c) F. J. Urban, B. S. Moore, and R. Breitenbach, *Tetra. Lett.*, **1990**, *31*, 4421. (d) M. P. DeNinno, P. A. McCarthy, K. C. Duplantier, C. Eller, J. B. Etienne, M. P. Zawistoski, F. W. Bengerter, C. E. Chandler, L. A. Morehouse, E. D. Sugarman, R. W. Wilkins, H. A. Woody, L. M. Zaccarro, *J. Med. Chem.*, **1997**, *40*, 2547. (e) C. Li, B. Yu, M. Liu, Y. Hui, *Carbohydr. Res.*, **1998**, *306*, 189. (f) S. Deng, B. Yu, Y. Hui, X. Han, *Carbohydr. Res.*, **1999**, *317*, 53.
3. R. B. Conrow, S. Bernstein, *J. Org. Chem.*, **1971**, *36*, 863.
4. This compound was obtained by treatment of O- (2,3,4,6-tetra-)-acetyl-α-D-glucopyranosyl)-(1→3)-1,2,4,6,-tetra-O-acetyl-D- glucopyranose (*Ref*.,K. Takeo, S. Kitamura, Y. Murata, *Carbohydr. Res.*, **1992**, *224*, 111.) with 33% HBr in HOAc in dichloromethane. ^{1}H NMR ($CDCl_3$, 300MHz): 6.62(d, 1H, 3.9Hz, H-1), 5.22-5.16(m, 2H, H-3′, H-4′), 5.13-5.00 (m, 2H, H-2′, H-4), 4.91(d, 1H, 1.8Hz, H-1′), 4.77(dd, 1H, 3.9Hz, 9.6Hz, H-2), 4.28-4.06(m, 4H, H-3, H-5, H-6a,b), 3.82(m, 1H, H-5′), 2.18, 2.15, 2.12, 2.09, 2.02, 1.95, (18H, 6s, H-OAc), 1.17(d, 3H, 6.3Hz, H-6″).
5. This compound was obtained by glucosylating 1,3,4,6-tetra-*O*-acetyl α, β-D-glucopyranose with 2, 3, 4-tri-*O*-benzoyl-α-L-rhamnopyranosyl trichloroacetimidate (*Ref*., S. Brennan, P. A. Finan, *J. Chem. Soc.*, **1970**, 1742.) to get 1,3,4,6-tetra-*O*-acetyl-2-*O*-(2,3,4-tri-*O*-benzoyl-α-L-rhamnopyranosyl) α,β-D-glucopyranose and then treated with 33% HBr in HOAc in dichloromethane. ^{1}H NMR ($CDCl_3$, 300MHz): 8.10-7.23(m, 15H, H-OBz), 6.51(d, 1H, 3.9Hz, H-1), 5.76-5.71(m, 2H, H-3′, H-4′), 5.61(t, 1H, 9.6Hz, H-3), 5.51(m, 1H, H-2′),

5.19-5.12(m, 2H, H-1′, H-4), 4.42-4.32(m, 3H, H-5′, H-5, H-6a), 4.14(m, 1H, H-6b), 3.87(dd, 1H, 9.6Hz, 3.9Hz, H-2), 2.12, 2.10, 2.06, (3s, 9H, H-OAc), 1.35(d, 3H, 6.0Hz, H-6″).

6. (a) D. Bednarczyk, W. Kaca, H. Myszka, L. Serwecinska, Z. Smiatacz A. Zaborowski, *Carbohydr. Res.*, **2000**, *328*, 249. (b) R. U. Lemieux, T. Takeda, B. Y. Chung, *Synthetic Methods for Carbohydrates*, Kadhem, H. S. E., Ed.; American Chemical Society: Washington, D. C. , **1977**, 90.
7. Selected 1H NMR data of **1e**, **1f**, **1g**, and **1h**: **(1e)** ($CDCl_3$, 300MHz): 5.34(d, 1H, 4.8Hz, H-6), 5.11-5.04(m, 4H, H-4′, H-2″, H-3″, H-4″), 5.00(dd, 1H, 8.1Hz, 9.6Hz, H-2′), 4.80(d, 1H, 1.8Hz, H-1″), 4.47(d, 1H, 8.1Hz, H-1′), 4.39(m, 1H, 16-H), 4.22-4.04(m, 2H, H-6′a,b), 3.86(m, 1H, H-5″), 3.78(t, 1H, 9.6Hz, H-3′), 3.56-3.33(m, 4H, H-3, H-26a,b, H-5″), 2.18, 2.16, 2.11, 2.10, 2.05, 1.96(6s, 18H, H-OAc), 1.18(d, 3H, 6.3Hz, H-6″), 1.00(s, 3H), 0.96(d, 3H, 6.9Hz), 0.78(d, 3H, 6.3Hz), 0.76(s, 3H). **(1f) (**$CDCl_3$, 300MHz): 8.10-7.25(m, 15H, H-OBz), 5.79(dd, 1H, 3.6Hz, 9.9Hz, H-3″), 5.65(t, 1H, 9.9Hz, H-4″), 5.55(t, 1H, 9.6Hz, H-3′), 5.48(dd, 1H, 1.5Hz, 3.3Hz, H-2″), 5.39(d, 1H, 4.5Hz, H-6), 5.14-5.12(m, overlap, 2H, H-1′, H-1″), 5.01(t, 1H, 9.6Hz, H-4′), 4.41(m, 1H, 16-H), 4.32-4.09(m, 4H, H-5′, H-6′a,b, H-5″), 3.81(d, 1H, 3.6Hz, 9.6Hz, H-2′), 3.57-3.33(m, 3H, H-3, H-26a,b), 2.16, 2.09, 2.03(9H, 3s, H-OAc), 1.31(d, 3H, 6.6Hz, H-6″), 1.10(s, 3H), 0.97(d, 3H, 6.9Hz), 0.80(s, 3H,), 0.77(d, 3H, 6.0Hz). **(1g)** ($CDCl_3$, 500MHz): 8.08-7.25(m, 15H, H-OBz), 5.78(dd, 1H, 3.5Hz, 10.0Hz, H-3″), 5.69(t, 1H, 10.0Hz, H-4″), 5.44(d, 1H, 4.5Hz, H-6), 5.41(dd, 1H, 1.5Hz, 3.5Hz, H-2″), 5.36(t, 1H, 9.5Hz, H-3′), 5.26(d, 1H, 1.5Hz, H-1″), 5.01(t, 1H, 9.5Hz, H-4′), 4.72(m, 1H, H-5″), 4.68(d, 1H, 8.0Hz, H-1′), 4.41(m, 1H, H-16), 4.30(dd, 1H, 5.5Hz, 15.5Hz, H-6′a), 4.10(dd, 1H, 2.5Hz, 15.5Hz, H-6′b), 3.84(d, 1H, 8.0Hz, 9.5Hz, H-2″), 3.74(m, 1H, H-5′), 3.66 (m, 1H, H-3), 3.47(m, 1H, H-26a), 3.38(t, 1H, H-26b), 2.15, 2.08, 2.03(3s, 9H, H-OAc), 1.32(d, 3H, 6.5Hz, H-6″), 0.95(d, 3H, 7.0Hz), 0.88(s, 3H), 0.77(d, 3H, 6.0Hz), 0.74(s, 3H). **(1h)** ($CDCl_3$, 300MHz): 7.88-7.73(m, 4H, H-Ph), 5.77(dd, 1H, 10.2Hz, 9.3Hz, H-3′), 5.47(d, 1H, 8.7Hz, H-1′), 5.22 (d, 1H, 4.2Hz, H-6), 5.16(t, 1H, 9.6Hz, H-4′), 4.42-4.25(m, 3H, H-16, H-2′, H-6′a), 4.14(m, 1H, H-6′b), 3.85(m, 1H, H-5′), 3.51-3.32(m, 3H, H-3, H-26a,b), 2.10, 2.03, 1.85(3s, 9H, H-OAc), 0.95(d, 3H, 6.9Hz), 0.88(s,3H), 0.77(d, 3H, 6.0Hz), 0.74(s, 3H).

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