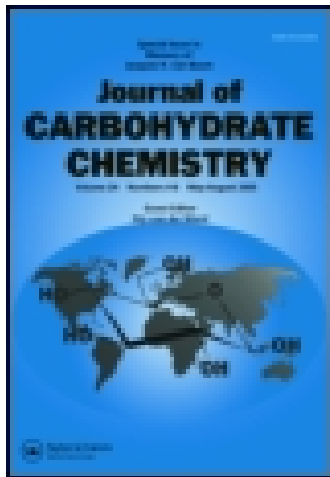


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PREPARATION OF GLYCOSYL DIMETHYLTHIOPHOSPHATES AND THEIR APPLICATION AS GLYCOSYL DONORS

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ABSTRACT

Benzyl- and acetyl-protected glycosyl dimethylthiophosphates were readily prepared from corresponding 1-hydroxyl sugars in good yield, and acted as very stable and efficient glycosyl donors in the construction of glycosidic bonds in the presence of various promoters.

INTRODUCTION

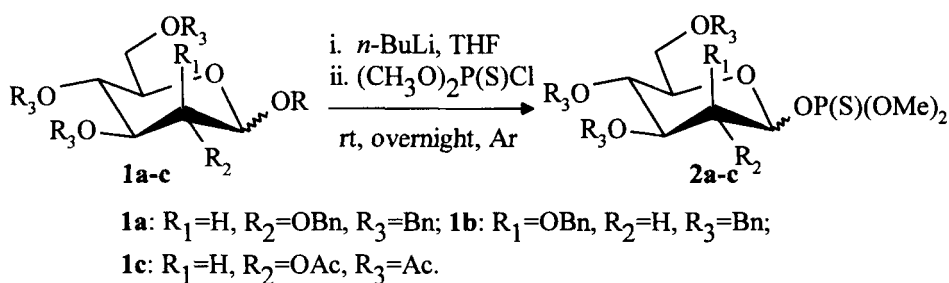
The rapidly growing interest in glycosides and oligosaccharides as constituents of biologically and pharmaceutically significant substances has stimulated enormous effort to develop potent glycosylation methods. It is recognized that the leaving group of a glycosyl donor is one of the most dominant parameters responsible for the efficiency of the glycosylation reactions.¹ One of the current topics in this area is the development of glycosyl donors bearing phosphorus-containing leaving groups, on the prospect that a glycosyl donor could be tailor-made by variation of substituents on the phosphorus atom. Indeed, a number of modifications on the phosphorus atom of the glycosyl donors have been investigated. These include glycosyl phosphites,² phosphate,³

phosphinimidate,⁴ phosphoroamidate,⁵ phosphinothioate,⁶ phosphorodithioate,⁷ and phosphorodiamidimido-thioate.⁸ All these endeavors to develop glycosyl donors with phosphorus-containing leaving groups are paving powerful ways to construct glycosidic bonds. From the viewpoint of how to get the glycosyl donors, this approach can be regarded as an important alternative to the glycosyl trichloroimidate method developed by R. R. Schmidt.^{1b} Herein, we wish to report the first preparation of glycosyl dimethylthiophosphates and their application as a new type of glycosyl donor.

RESULTS AND DISCUSSION

2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl dimethylthiophosphate (**2a**), 2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl dimethylthiophosphate (**2b**), and 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl dimethylthiophosphate (**2c**) were readily prepared in good yield by treatment of the corresponding 1-hydroxyl sugars (**1a**,⁹ **1b**,⁹ **1c**^{2c}) with dimethyl chlorothiophosphate in the presence of *n*-butyllithium (1.2 equiv) in tetrahydrofuran (THF). The results are shown in Scheme 1 and Table 1. This reaction, which could be completed at room temperature overnight, was a little sluggish compared with the reaction of the corresponding 1-*O*-lithium sugars with dimethylphosphinothioyl chloride (-30 °C, 1h) to produce glycosyl dimethylphosphinothioate.⁶ The α anomers were predominantly produced, given the anomeric effect of the corresponding 1-*O*-lithium sugars. It is noteworthy here that these glycosyl dimethylthio-phosphates (**2a-c**) were extremely stable, and were not found to undergo any detectable changes on the shelf without any care for half a year.

On the other hand, the stable glycosyl dimethylthiophosphates (**2a-c**) could serve as efficient glycosyl donors in the presence of various Lewis acid promoters under mild conditions, as shown in Scheme 2 and Table 2. By using benzyl protected glycosyl dimethylthiophosphate **2a** as a glycosyl donor and methyl 2-*O*-benzoyl-4,6-benzylidene- α -D-glucopyranoside **3**¹⁰ as an acceptor, (because the α,β anomers of the glycosylation product **8** could be easily detected by TLC), various promoters were screened (entries 1-5). Under the same conditions (CH₂Cl₂, rt, overnight), TMSOTf and AgOTf were found more effective than other thiophilic Lewis acids, such as HgCl₂, NIS, and MeOTf. By

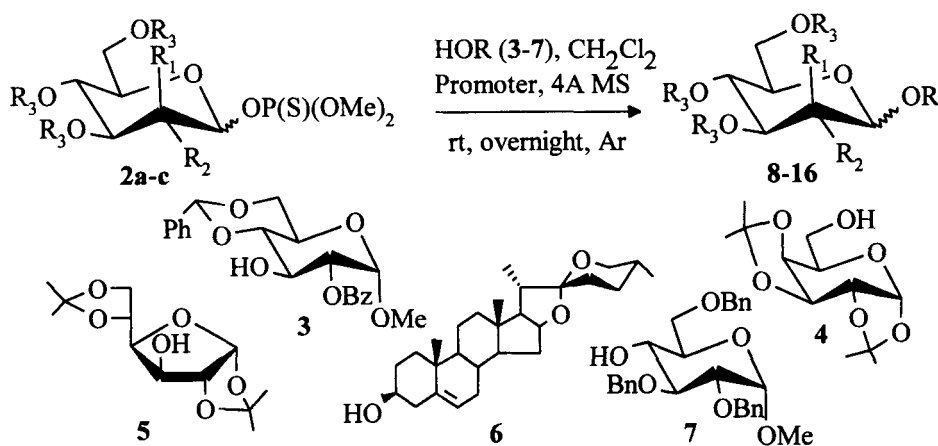


Scheme 1

Table 1. Preparation of Glycopyranosyl Dimethylthiophosphates (2a-c)

Reactant	Base	Temperature ($^{\circ}\text{C}$)	Time (h)	Product	Yield (%) ^a	$\alpha : \beta$ ^b
1a	Et_3N	-78, then rt	24	no		
1a	$n\text{-BuLi}$	-78	24	no		
1a	$n\text{-BuLi}$	-30	18	2a	trace	
1a	$n\text{-BuLi}$	-30, then rt	2	2a	< 10	
1a	$n\text{-BuLi}$	-30, then rt	12	2a	86.1	75:25
1b	$n\text{-BuLi}$	-30, then rt	overnight	2b	71.0	α
1c	$n\text{-BuLi}$	-30, then rt	overnight	2c	51.2	83:17

a. Isolated yield; b. Determined by ^1H NMR, ^{31}P NMR, **2a** and **2b** were also determined by HPLC (SiO₂ column, 4.6 \times 250mm, *n*-Hexane/Ethyl acetate: 100/10 - 100/15, flow rate: 1.5 mL/min, UV 254 nm).



Scheme 2

Table 2. The Glycosylation Reactions of Glycosyl Dimethylthiophosphates (2a-c)^a

Entry	Donor	Acceptor	Promoter	Product ^b	Yield % ^c	$\alpha : \beta^d$
1	2a	3	HgCl ₂	8	22.5	40 : 60
2	2a	3	NIS	8	26.8	50 : 50
3	2a	3	MeOTf	8	30.2	50 : 50
4	2a	3	TMSOTf	8	62.5	89 : 11
5	2a	3	AgOTf	8	55.0	67 : 33
6	2a	4	TMSOTf	9 ^{2e}	60.0	25 : 75
7	2a	4	AgOTf	9	94.0	67 : 33
8	2a	5	TMSOTf	10 ⁸	53.0	60 : 40
9	2a	6	AgOTf	11	85.7	α only
10	2a	7	TMSOTf	12 ^{2d}	24.3	65 : 35
11	2a	7	AgOTf	12	58.2	57 : 43
12	2a	7	AgOTf + NIS	12	82.0	75 : 25
13	2b	4	AgOTf	13 ^{6c}	80.0	72 : 28
14	2b	7	AgOTf	14 ^{2d}	78.0	α only
15	2c	4	AgOTf	15 ¹¹	30.0	β only
16	2c	6	AgOTf	16	13.0	β only

a. Donor/accepter/promoter molar ratio = 1/1/1; b. The known products gave satisfactory physical datas with literatures reported; c. Isolated yield; d. Determined by ¹H NMR and HPLC (the same conditions as used in Table 1).

employing TMSOTf or AgOTf as the promoter, 1,2:3,4-di-*O*-isopropylidene- α -D-galactopyranose (**4**), 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose (**5**), and diosgenin (**6**) were glycosylated by thiophosphate **2a** in excellent yields (entries 6-9). When methyl 2,3,6-tri-*O*-benzyl- α -D-glucopyranoside (**7**), a less active acceptor, was used, TMSOTf was found not to be strong enough to efficiently promote the corresponding glycosylation reaction (entry 10), while AgOTf was still effective (entry 11). The combination of AgOTf and NIS (0.5 : 0.5 molar ratio) was shown to be much more effective, 82% yield of the glycosylation product **12** was obtained (entry 12). Under the same conditions with AgOTf as the promoter, 2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl dimethylthiophosphate (**2b**) was also detected as an efficient glycosyl donor (entries 13-14) and excellent yields of the products were furnished. Finally, 2,3,4,6-tetra-*O*-acetyl-D-

glucopyranosyl dimethylthiophosphate (**2c**) was briefly examined as a glycosyl donor. However, the acetylated glycosyl thiophosphate **2c** was shown much less effective than the benzylated donors under the same conditions (entries 15-16), and considerable amounts of acetylated alcohol acceptors (30% and 52% respectively) were detected. In all these glycosylation reactions of the glycosyl dimethylthiophosphates, the α,β anomer outcomes of the glycosylation products were found, although effected by the promoters used (entries 6, 7), to be mainly determined by the properties of the donor and acceptor themselves, (the extreme examples are entries 9 and 14). Therefore, the above glycosylation reactions were more likely to proceed through the glycosyl oxocarbenium intermediates.

It is well documented that solvents, such as CH_3CN , have an important impact on the stereoselectivity of a glycosylation reaction.¹² We also examined the solvent effects on glycosylation using glycosyl thiophosphates. In the reaction of **2a** with **4** under the same conditions with promoter AgOTf, CH_2Cl_2 , toluene, and CH_3CN were used as solvent in parallel reactions. The results are listed in Table 3. There was little solvent effect found on the stereoselectivity of the glycosylations using glycosyl thiophosphate **2a**. But this reaction was greatly retarded by using CH_3CN as solvent, which could only be carried out at 55 °C.

In conclusion, benzyl- and acetyl- protected glycosyl dimethylthiophosphates were readily prepared, and employed as novel glycosyl donors. The improvement on the stereoselectivity using glycosyl thiophosphates and the application in the oligosaccharides syntheses are in progress.

EXPERIMENTAL

General Methods. Solvents were purified in the usual way. Melting points are uncorrected. Optical rotations given in units of $10^{-1}\text{deg cm}^2\text{g}^{-1}$, were determined with a Perkin-Elmer Model 241 MC polarimeter at 22 °C. ^1H NMR spectra were recorded on Bruker AM-300 or AM-600 spectrometers using TMS as internal standard. Mass spectra were taken on HP5989A, and VG Quattro MS/MS spectrometers. TLC was performed using silica gel plates HF254 (Qingdao, China). Flash column chromatography was performed using silica gel (400 mesh, Qingdao, China).

Table 3. Solvent Effects on the Glycosylation Reaction of 2a and 4

Entry	Solvent	Temperature (°C)	Time	Yield (%) ^a	$\alpha : \beta$ ^b
1	CH ₂ Cl ₂	-78, then rt	overnight	94.0	70 : 30
2	Toluene	-78, then rt	overnight	95.0	65 : 35
3	CH ₃ CN	-78, then rt	overnight	trace	
4	CH ₃ CN	55	overnight	52.4	64 : 36

a. Isolated yield. b. Determined by ¹H NMR and HPLC (the same conditions as described in Table 1).

Typical procedure for the preparation of glycosyl dimethylthiophosphates (2a-c). To a stirred dry THF solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose **1a** (2.16 g, 4.0 mmol) was added 2.0 mL of *n*-BuLi (2.5 M in hexane, 1.2 equiv) at -30 °C under Ar. After stirring for 1 h at the same temperature, dimethyl thiophosphate chloride (0.61 mL, 5 mmol, 1.25 equiv) was added to it and the mixture was warmed up naturally to room temperature overnight. After the reaction was completed (TLC, about 12-14 h), the solution was poured into water and extracted with ethyl ether (3 × 60 mL). The organic layer, washed with water and brine, was dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was separated by the silica gel column chromatography (petroleum ether : ethyl acetate, 10 : 1) to give thiophosphates **2a**.

2,3,4,6-Tetra-*O*-benzyl- α/β -D-glucopyranosyl Dimethylthiophosphate (2a).

White solid; Yield: 86.1%; α/β : 3/1; R_f = 0.75 (petroleum ether : ethyl acetate, 3:1); ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.11 (m, 20 H, 4 × C₆H₅), 5.99 (dd, 0.75 H, $J_{1,2}$ = 3.2 Hz, $J_{1,P}$ = 9.8 Hz, α -H-1), 5.23 (dd, 0.25 H, $J_{1,2}$ = $J_{1,P}$ = 9.0 Hz, β -H-1), 4.97-4.42 (m, 8 H, 4 × PhCH₂), 3.93 (t, 2H, $J_{2,3}$ = $J_{3,4}$ = $J_{4,5}$ = 9.3 Hz, H-3, H-4), 3.69 (d, 6H, J_{P,OCH_3} = 13.7 Hz, 2 × OCH₃), 3.74-3.61 (m, 4H, H-2, H-5, H-6a, H-6b); ³¹P NMR (CDCl₃) δ 94.99 (β), 94.46 (α); EI-MS: m/z 431, 339, 253, 181, 91 (100%).

Anal. Calcd for C₃₆H₄₁O₈PS • H₂O (682.82): C, 63.32; H, 6.36. Found: C, 63.23; H, 6.40.

2,3,4,6-Tetra-*O*-benzyl- α -D-mannopyranosyl Dimethylthiophosphate (2b).

White solid; Yield: 71.0%; α only; R_f = 0.47 (petroleum ether : ethyl acetate, 5:1), [α]_D²²

+ 60.5° (*c* 0.04, CHCl₃), ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.11 (m, 20 H, 4 × C₆H₅), 5.83 (dd, 1H, J_{1,2} = 1.9 Hz, J_{1,P} = 9.0 Hz, H-1), 4.91-4.48 (m, 8H, 4 × PhCH₂), 4.03 (t, 1H, J_{3,4} = J_{4,5} = 9.6 Hz, H-4), 3.93 (d, 1H, J_{2,3} = 3.4 Hz, H-2), 3.87 (dd, 1H, H-3), 3.80-3.72 (m, 3H, H-5, H-6), 3.63 (dd, 6H, J_{P,OCH₃} = 13.6 Hz, 2 × OCH₃); ³¹P NMR (CDCl₃) δ 70.21; EI-MS: *m/z* 633 (M-1)⁺, 521, 431, 253, 181, 91 (100%).

Anal. Calcd for C₃₆H₄₁O₈PS (664.80): C, 65.04; H, 6.23. Found: C, 65.24; H, 6.40.

2,3,4,6-Tetra-*O*-acetyl-α/β-D-glucopyranosyl Dimethylthiophosphate (2c).

White solid; Yield: 64.5%; α/β: 4/1; R_f = 0.60 (petroleum ether : ethyl acetate, 3:2); ¹H NMR (300 MHz, CDCl₃) δ 5.94 (dd, 0.8 H, J_{1,2} = 3.4 Hz, J_{1,P} = 9.8 Hz, α-H-1), 5.32 (dd, 0.2 H, J_{1,2} = 8.1 Hz, J_{1,P} = 10.1 Hz, β-H-1), 5.24 (t, 1 H, J_{3,4} = J_{4,5} = 9.3 Hz, H-4), 5.11 (m, 1H, J_{2,3} = 8.1 Hz, H-2), 5.04 (t, 1H, H-3), 5.00 (m, 0.8 H, α-H-5), 4.24 (dd, 1H, J_{5,6a} = 5.1 Hz, J_{6a,6b} = 12.4 Hz, H-6a), 4.14 (dd, 1H, J_{5,6b} = 2.3 Hz, H-6b), 3.80 (m, 0.2 H, β-H-5), 3.78 (d, 3H, J_{P,OCH₃} = 10.9 Hz, OCH₃), 3.69 (d, 3H, J_{P,OCH₃} = 9.4 Hz, OCH₃), 2.05, 2.04, 2.01, 1.99 (4 × s, 4 × 3H, 4 × OAc); ³¹P NMR (CDCl₃) δ 71.08(α), 71.30(β); EI-MS: *m/z* 413 (M-OAc)⁺, 331, 271, 221, 169, 43 (100%).

Anal. Calcd for C₁₆H₂₅O₁₂PS (472.44): C, 40.67; H, 5.34. Found: C, 40.72; H, 5.38.

Typical procedure for the glycosylation reactions. A mixture of glycosyl dimethylthiophosphate donor (0.1 mmol), acceptor (0.1 mmol) and 4Å MS (150 mg) in dry CH₂Cl₂ (5 mL) was stirred at room temperature for 1 h under Ar, then cooled to -78 °C. To the above stirred suspension was added promoters (1.0 equiv., for AgOTf, dissolved in 2 mL of dry toluene first), then it was warmed up slowly to room temperature overnight. Usual workup and purification by silica gel column chromatography to afford the glycosylation product.

Methyl 2-*O*-Benzoyl-3,4-*O*-benzylidene-3-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-α-D-glucopyranoside (8). Syrup, Yield: 55%, α/β: 2/1, α and β anomers were separated by silica gel column chromatography. **α-anomer:** R_f = 0.41 (petroleum ether : ethyl acetate, 5:1); [α]_D²² + 45.3 (*c* 0.39, CHCl₃); ¹H NMR (600 MHz,

CDCl₃) δ 7.96-6.82 (m, 30 H, 6 \times C₆H₅), 5.54 (d, 1H, $J_{1',2'} = 3.6$ Hz, H-1'), 5.37 (s, 1H, PhCH), 5.21 (dd, 1H, $J_{1,2} = 3.8$ Hz, $J_{2,3} = 9.8$ Hz, H-2), 4.96 (d, 1H, H-1), 4.80, 4.56 (AB, 1H each, $J = 10.8$ Hz, PhCH₂), 4.53 (dd, 1H, $J_{2,3} = J_{3,4} = 9.4$ Hz, H-3), 4.54 and 4.17 (AB, 1H each, $J = 11.2$ Hz, PhCH₂), 4.46 and 4.28 (AB, 1H each, $J = 12.0$ Hz, PhCH₂), 4.45 and 4.25 (AB, 1H each, $J = 12.4$ Hz, PhCH₂), 4.21 (dd, 1H, $J_{5,6a} = 4.7$ Hz, $J_{6a,6b} = 10.3$ Hz, H-6a), 3.90 (m, 1H, $J_{4,5} = 9.9$ Hz, $J_{5,6a} = 5.0$ Hz, $J_{5,6b} = 14.5$ Hz, H-5), 3.84 (dd, 1H, $J_{3,4} = 9.3$ Hz, H-4), 3.71 (m, 3 H, H-3', H-4', H-6b), 3.45 (dd, 1H, $J_{1',2'} = 3.6$ Hz, $J_{2',3'} = 9.9$ Hz, H-2'), 3.44-3.43 (m, 2 H, H-5', H-6a'), 3.32 (s, 3H, OCH₃), 2.19 (dd, 1H, $J_{5',6a'} = 2.8$ Hz, $J_{6a',6b'} = 10.6$ Hz, H-6b'); EIMS: m/z 907 (M-1)⁺, 712, 679, 573, 431, 181, 91(100%). **β -anomer:** $R_f = 0.48$ (petroleum ether : ethyl acetate, 5:1); $[\alpha]_D^{22} +9.2$ (c 0.17, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.96-7.04 (m, 30 H, 6 \times C₆H₅), 5.53 (s, 1H, PhCH), 5.08 (d, 1H, $J_{1,2} = 3.7$), 5.21 (dd, 1H, $J_{2,3} = 9.8$ Hz, H-2), 4.79-4.26 (m, 10H), 3.96-3.73 (m, 4H), 3.60-3.40 (m, 9H); ¹H NMR (600 MHz, CDCl₃, the 4',6'-*O*-benzylidene group was found completely hydrolyzed after one week in CDCl₃ when doing NMR) δ 10.01 (s, 1H, PhCHO), 7.96-6.89 (m, 30 H, 6 \times C₆H₅), 5.07 (d, 1H, $J_{1,2} = 3.7$ Hz, H-1), 5.05 (dd, 1H, $J_{2,3} = 9.6$ Hz, H-2), 4.77 and 4.62 (AB, 1H each, $J = 10.9$ Hz, PhCH₂), 4.74 and 4.64 (AB, 1H each, $J = 10.9$ Hz, PhCH₂), 4.53 and 4.49 (AB, 1H each, $J = 11.9$ Hz, PhCH₂), 4.58 (d, 1H, $J_{1',2'} = 7.7$ Hz, H-1'), 4.47 (t, 2H, $J = 12.0$ Hz, PhCH₂), 4.15 (t, 1H, $J_{2,3} = J_{3,4} = 9.0$ Hz, H-3), 3.92 (dd, 1H, $J_{5,6a} = 3.6$ Hz, $J_{6a,6b} = 11.6$ Hz, H-6a), 3.83 (dd, 1H, $J_{5,6b} = 4.9$ Hz, H-6b), 3.74 (m, 1H, H-5), 3.69 (t, 1H, H-4), 3.68 (t, 1H, $J_{6a',6b'} = 9.7$ Hz, H-6a'), 3.59 (t, 1H, $J_{2',3'} = 8.3$ Hz, H-3'), 3.58 (dd, 1H, $J_{5',6b'} = 6.7$ Hz, H-6b'), 3.52 (t, 1H, $J_{3',4'} = J_{4',5'} = 9.2$ Hz, H-4'), 3.41 (t, 1H, $J_{1',2'} = J_{2',3'} = 8.2$ Hz, H-2'), 3.36 (s, 3H, OCH₃).

Anal. Calcd for C₅₅H₅₆O₁₂ (909.04): C, 72.67; H, 6.21. Found: C, 72.75; H, 6.15.

Diosgenyl 2',3',4',6'-Tetra-*O*-benzyl- α -D-glucopyranoside (11). Syrup; Yield: 85.7%; $R_f = 0.64$ (petroleum ether : ethyl acetate, 5 : 1); $[\alpha]_D^{22} - 3.7$ (c 0.32, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 7.36-7.13 (m, 20H, 4 \times C₆H₅), 5.28 (br., 1H, H-6), 5.00, 4.81 (AB each, 2H, $J = 9.9$ Hz, PhCH₂), 4.94 (d, 1H, $J_{1',2'} = 3.5$ Hz, H-1'), 4.83, 4.47 (AB each, 2H, $J = 10.2$ Hz, PhCH₂), 4.76, 4.65 (AB each, 2H, $J = 9.8$ Hz, PhCH₂), 4.60, 4.55 (AB each, 2H, $J = 12.1$ Hz, PhCH₂), 4.42 (m, 1H, H-16), 4.00 (t, 1H, $J_{2',3'} = J_{3',4'} = 9.3$ Hz, H-

3'), 3.88 (m, 1H, H-5'), 3.74 (dd, 1H, $J_{5',6a'} = 3.7$ Hz, $J_{6a',6b'} = 10.6$ Hz, H-6a'), 3.64 (dd, 1H, H-6b'), 3.63 (t, 1H, $J_{4',5'} = 9.2$ Hz, H-4'), 3.55 (dd, 1H, $J_{1',2'} = 3.6$ Hz, H-2'), 3.49-3.38 (m, 3H, 2 × H-26, H-3), 1.03 (s, 3H, CH₃-19), 0.98 (d, 3H, CH₃-21), 0.80 (s, 3H, CH₃-18), 0.75 (d, 3H, CH₃-27); EI-MS: m/z 773, 687, 615, 537, 91(100%).

Anal. Calcd for C₆₁H₇₆O₈ (937.27): C, 78.17; H, 8.17. Found: C, 78.26; H, 8.19.

Diosgenyl 2',3',4',6'-tetra-*O*-acetyl- β -D-glucopyranoside (16). White solid; Yield: 13%; $R_f = 0.46$ (petroleum ether : ethyl acetate, 2:1); $[\alpha]_D^{22} - 61.4$ (c 1.0, CHCl₃); mp 88-89; ¹H NMR (300 MHz, CDCl₃) δ 5.32 (br., 1H, H-6), 5.17 (t, 1H, $J_{2',3'} = J_{3',4'} = 9.4$ Hz, H-3'), 5.06 (t, 1H, $J_{4',5'} = 9.5$ Hz), 4.97 (dd, 1H, $J_{1',2'} = 8.1$ Hz, H-2'), 4.57 (d, 1H, H-1'), 4.39 (m, 1H, H-16), 4.24 (dd, 1H, $J_{5',6'a} = 6.2$ Hz, $J_{6'a,6'b} = 12.1$ Hz), 4.08 (dd, 1H, $J_{5',6'b} = 2.7$ Hz), 3.67 (m, 1H, H-5'), 3.44 (m, 2H, H-26), 3.36 (m, 1H, H-3), 2.08, 2.05, 2.02, 2.00 (s each, 12H, 4 × OAc); EI-MS: m/z 745(M + 1), 685, 601, 397, 324, 282 (100%).

Anal. Calcd for C₄₁H₆₀O₁₂ (744.92): C, 66.11; H, 8.12. Found: C, 66.91; H, 8.32.

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