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A New Highly Regioselective Reaction of Unprotected Sugars for Chemical Synthesis of Methyl-6-D-acyl-D-glycopyranosides by Mean of Chlorophosphoric Acid Diethyl Ester[$(C_2H_5O)_2P(:O)Cl$] as Condensing Reagent

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A NEW HIGHLY REGIOSELECTIVE REACTION OF UNPROTECTED SUGARS FOR CHEMICAL SYNTHESIS OF METHYL-6- D -ACYL-D-GLYCOPYRANOSIDES BY MEAN OF CHLOROPHOSPHORIC ACID DIETHYL ESTER[(C2H5O)2P(:O)Cl] AS CONDENSING REAGENT

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Abstract: A new methodology which allows the regioselective acylation of no protected methyl-D-glycopyranosides at the primary hydroxy group is described.Thus,a new synthetic procedure is presented to synthesize 6-acyl-methyl-glycopyranosides from unprotected glycopyranosides by means of (EtO)2P:OCl as condensing reagent.

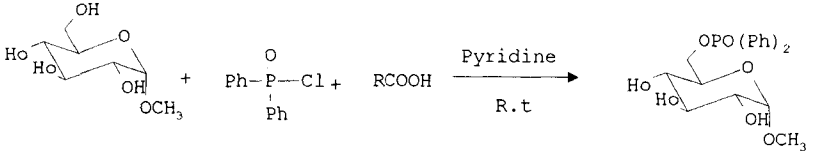
Fatty acid esters of carbohydrates constitute an interesting gruop of nonionic surfactants. These surface-active materials exhibit highly useful properties because of their surface-active propertiesand being easily degraded in nature [1]. The possibilities for preparing esters of carbohy-drates have , accordingly, been extensively studied in the past and the selective derivatizationof only one out of multiple hydroxy functions of similar reactivity in carbohydrate moleculeshas been an exciting and challenging problem in carbohydrate chemistry, for instance,the functionalization of unprotected sugars with base-labile groups, such as benzoyl,via the classic acylation precedure with acyl chloride in pyridine, affords a mixture of polysubstituted derivatives[2-6]. Recently, we have developed new methodologies to synthesize 6-acyl-D-glycopyranosides from unprotected glycopyranosides using easily synthesized reagents, acyl-p-nitrothiophenol esters and acyl-2,4-dinitrophenol esters as

acylating reagents resulting in high regioselectivities[7] and as a continued work to develop a new methodology of synthesis of bio-activity sugars esters, now we report the sythesis of 6-acyl-D-glycopyranosides from non protected glycopyranosides by means of chlorophosphoric acid diethyl ester as condensing reagent. The procedure of the experiments was two-step, one-pot procedures for the conversion of carboxylic acids and carbohydrates into sugar esters. We attempted to employ one-step,one-pot procedure to synthesize sugar esters when diphenylphosphinic chloride was used as condensing reagent. The main product which we had gotton was only (2) that obtained by interaction of the condensing agent with the primary hydroxy of the glycopyranosides as scheme 1

This forced us to employ a two-step, one -pot procedure to synthesize sugar esters when chlorophosphoric acid diethyl ester used as condensing agent. Fatty acids were first activated by condensing agent, chlorophosphoric acid diethyl ester(1) as scheme 2 in dichloromethane in the prensence of triethylamine as the base at room temperature to obtain the (3).

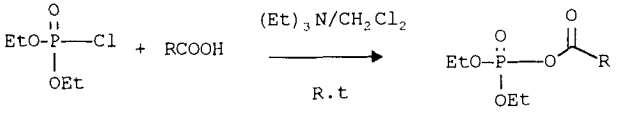
The solubility properties of carbohydrates have always favoured the use of pyridine or

Scheme 1



(2)

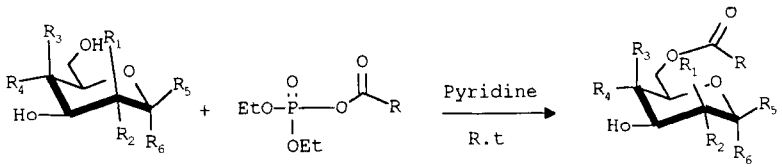
Scheme 2



(3)

DMF as solvent either chemical or enzymatic transformation into acyl derivatives, thus, glycopyranosides solved in anhydrous pyridine were added into the (3) to selective acylating of methyl-D-glycopyranosides as scheme 3 at room temperature.

Scheme 3



(1) R1=H, R2=OH
R3=H, R4=OH
R5=H, R6=OCH3
(2) R1=OH, R2=H
R3=H, R4=OH
R5=H, R6=OCH3
(3) R1=H, R2=OH
R3=H, R4=OH
R5=OCH3, R6=H

(1a-1d)
(2a-2d)
(3a-3d)

When long fatty acids are allowed to react with glycopyranosides in the presence of chlorophosphoric acid diethyl ester as condensing agent, only isolated products correspond to 6-acyl-D-glycoyranosides are reported.TLC analysis of the corde material showed, also

Table 1 Preparation of 6-acyl-methyl-α-D-glucopyranoside(1a-1d) using (1) as condensing agent.

Run	Fatty acid	Temp.(^{0}C)	R.t (hr)	Yield(%)
1a	Undecanoic acid	25	3	50.2
1b	Palmitic acid	25	3	49.2
1c	Stearic acid	25	4	44.1
1d	Arachidic acid	25	3	56.0

Note: Yield is isolated by column chromatography.

Table 2 Preparation of 6-O-methy- α-D-mannopyranoside(2a-2d)using (1) as condensing agent.

Run	Fatty acid	Temp.(^{0}C)	R.t(hr)	Yield(%)
2a	Undecyenoic acid	25	3	48
2b	Palmitic acid	25	3	59.1
2c	Stearic acid	25	4	60.3
2d	Arachidic acid	25	4	54.9

Note: Yield is isolated by column chromatography.

the presence traces of other derivatives, which have not been isolated and characterized. Detailed results are given in table1-3.

Table 3 Preparation of 6-acyl-methyl-β-D-galacopyranosides(3a-3d)using (1) as condensing agent.

Run	Fatty acid	Temp.(^{0} C)	R.t(hr)	Yield(%)
3a	Undecyenoic acid	25	3-4	74.5
3b	Palmitic acid	25	3-4	75.9
3c	stearic acid	25	4	42.4
3d	arachidic acid	25	4	55.5

Note:Yield is isolated by column chromatography

The structure of the compounds has been confirmed by ^{1}HNMR or EIMS and fast-atom-bombardment mass spectrometry(FABMS).In particular, the monoacylated glycopyranosides showed a downfield shift for 6-H protons 0.7-1 ppm, relative to methyl-D-glycopyranosides.Further evidence for the structure of the monoacylated glycopyranosides was obtained ^{13} CNMR experiments.The spectra of the 6-acylated glycopyranosides showed a downfield shift for the primary carbon of the monoacylated glycopyranosides.In Conclusion, employing the methodology described herein, highly regioselective acylation of unpropected glycopyranosides were performed at the primary hydroxyl group, using the versatile chlorophosphoric acid diethyl ester as condensing agent, resulting in high yield.

Experimental

General Methods and Materials----------Chlorophosphoric acid ethyl ester[(ethyl)P(O:)Cl] is a commerical agent purchased from TOKYYO Kasei Chemical Co. Pyridine was distilled from potassium hydroxide,dichloromethane was distilled from calcium hydride.Glass-backed silica gel TLC plates(silica gel F254,0.2-mm thickness) were supplied by Qing Dao, China.Chromatrography was performed on silica gel H,400 mesh, from Qing Dao,China.^{1} HNMRspectra were measured at Bruker AMX-300MHz

spectrometer with tertamethylsilane as internal standard and hexadeuteriodimethyl sulfoxide or hexadeuterioacetone as solvent.FAB and EI mass spectra were obtained on a VGQuattroMS/MS spectrometer.Samples were dissolved in glycerol as matrix.

General Procedure for acylation of glycopyranosides with (EtO)2P(:O)Cl as condensing agent.

Compound(1)(310mg 1.8mmol) was added to a solution of the fatty acid (1.64mmol) and triethylamine(2.46mmol) in dichloromethane (10ml).The suspension was stirred at room temperature for 3-4hr, a solution of the glycopyranosides (3.28mmol) in anhydrous pyridine(10ml) was then added to the suspension and the mixture was continuely stirred at room temperature for anther 3-4hr, until a nearly complete conversion of the acids was achieved[TLC, Petroleum benzine(60-90)-Ethyl acetate-Methanol(4:1:0.6,V/V)]. Saturated aq.sodium hydrogen carbonate (30ml) was then added and the mixture was extracted with dichloromethane (4X20ml).The organic layers evaporated to dryness(the pyridine present was removed by azeotropic distillation with toluene),afforded oily residues,which were purified by column chromatography[Potroleum benzine-Ethyl actate -Methanol(4:1:0.6)]to give purified syrups or amorphous pyranosides which was finally recrystallised from acetone,acetone-petroleum benzine, ethyl acetate.

Methyl 6-O-undecanoyl-α-D-glucopyranoside(1a)

Rf=0.44. m.p 84-85 ^{0}

FABMS(m/e): 363(M^{+}+1),331(M^{+}-OCH_3),313,197, 187, 169($C_{10}H_{21}CO^{+}$)(100%).

^{1} HNMR(DMSO):4.10-4.50ppm(1H, J=3.5Hz)4.40-4.20ppm(dd 1H J=10.5Hz H-6 J=7.4Hz)4.10-4.00ppm(dd 1H J=6.7Hz J=11.6Hz H-6') 3.60-3.50ppm(t 1H J=8.1Hz J=7.4Hz) 3.40-3.25Hz(m 7H) 3.20-3.10ppm(dd 1H J=3.6Hz J=9.6Hz) 3.10-3.00ppm (t 1H J=9.4Hz J=9.1Hz)2.40-2.20ppm(t 2H J=7.2Hz J=7.2Hz)1.65-1.50ppm(t 2H) 1.40-1.20ppm(s 14H)0.90-0.80ppm(t 3H J=5.9Hz J=6.8Hz).

Methyl 6-O-palmitoyl-α-D-glucopyranoside(1b)

Rf=0.21.m.p. 81-82 ^{0}

FABMS(m/e): 456(M^++Na+1),401(M^+-OCH_3),239($C_{15}H_{31}CO^+$),98(100%)

^{1} HNMR(DMSO):4.60-4.50ppm(d 1H J=3.6Hz) 4.35-4.25ppm(dd 1H J=11.4Hz J=3.8Hz) 4.10-4.00ppm(dd 1H J=6.3Hz J=11.2Hz)3.60-3.50ppm(t 1H J=8.8Hz J=7.1Hz) 3.40-3.25ppm(m 7H) 3.25-3.15ppm(dd 1H J=3.6Hz J=9.6Hz)3.10-3.00ppm (t 1H J=9.5Hz J=9.0Hz)2.30-2.20ppm(t 2H J=7.4Hz J=7.3Hz)1.60-1.50ppm(t 2H) 1.30-1.20ppm(s 24H)0.90-0.80ppm(t 3H J=6.4Hz J=6.5Hz).

Metthyl 6-O-stearoyl-α-D-glucopyranoside(1c)

Rf=0.40. m.p.87-89 ^{0}

FABMS(m/e): 484(M^++Na+1),430,412,267($C_{17}H_{35}CO^+$),93(100%).

EIMS(m/e):429(M^+-OCH_3),411,397,267($C_{17}H_{35}CO^+$)(100%),239,217,186,145,126,98,57, 43.

^{1} HNMR(DMSO):4.85-4.70ppm(d 1H J=3.9Hz H-1), 4.60-4.50ppm(dd 1H J=4.3Hz J=12.6Hz H-6) 4.30-4.15ppm(dd 1H J=2.1Hz J=12.3Hz H-6')3.80-3.60ppm(m 2H $H_{4\text{-}5}$)3.60-3.50ppm(dd 1H J=3.3Hz J=9.4Hz H-2) 3.40ppm(s 3H OCH_3) 3.39-3.30ppm (m 1H H-3) 2.50-2.30ppm(t 2H J=7.5Hz J=7.56Hz-$COCH_2$-)1.80-1.60ppm(m 2H) 1.40-1.20ppm(s 28H) 0.90-0.80ppm(t 3H J=6.4Hz J=6.9Hz).

^{13}**CNMR($CHCl_3$)**: **Methyl 6-stearoyl-α-D-glucopyranoside:**(ppm) 99.35,77.21,74.44, 72.30,69.90,62.90(CH_2OCO),55.45.

Methyl -α-D-glucopyranoside:99.49,73.22,71.81,70.18,60.82(CH_2OH)54.15.

Methyl 6-O-arachidoyl-α-D-glucopyranoside(1d).

Rf=0.22.m.p.87-88 ^{0}

EIMS(m/e): 457(M^+-OCH_3),440,295($C_{19}H_{39}CO^+$),277,262,185,145,129,98,57(100%).

^{1} HNMR(SMSO):5.20-5.00ppm(d 1H J=5.8Hz OH)4.90-4.80ppm(d 1H J=4.8Hz OH) 4.80-4.70ppm(d 1H J=6.5Hz OH)4.60-450ppm(d 1H J=3.5Hz)4.40-4.25ppm(dd 1H J=2.3Hz J=11.6Hz H-6)4.10-4.00ppm(dd 1H J=6.9Hz J=11.1Hz)3.70-3.20ppm(m 7H)3.10-3.00ppm(t 1H)2.40-2.20ppm(t 2H J=7.2Hz J=7.3Hz -$COCH_2$-)1.60-1.50ppm(m 2H)1.40-1.20ppm(s 32H)0.90-0.80ppm(t 3H J=6.1Hz J=6.8Hz).

Methyl 6-O-undecyenoyl-α-D-mannopyranoside(2a).

R_f=0.22.m.p 47-49 ^{0} .

EIMS(m/e):329(M^+-OCH_3),311,297,279,261,167($C_{10}H_{19}CO^+$),149,98,83,55(100%),43.

^{1} HNMR(DMSO): 5.00-4.85ppm(m 2H)4.65-4.60ppm(d 1H J=1.3Hz) 4.55-4.40ppm(dd 1H J=5.0Hz J=12.0Hz) 4.30-4.20ppm(dd 1H J=5.0Hz J=12.3Hz) 4.20-4.15ppm(dd 1H J=7.1Hz J=7.1Hz)3.90-3.80ppm(m 2H)3.70-3.60ppm(m 1H) 3.50-3.40ppm(s 3H OCH_3) 2.40-2.30ppm(t 2H J=7.1Hz J=7.3Hz)2.10-1.90ppm(dd 2H J=6.80Hz J=6.80Hz)1.70-1.50ppm(m2H)1.40-1.30ppm(m 10H).

Methyl 6-O-palmitoyl-α-D-mannopyranosides(2b).

R_f=0.23.m.p.49-50 ^{0} .

FABMS(m/e):456(M^++Na+1),239,($C_{15}H_{31}CO^+$),98(100%).

^{1} HNMR(DMSO):4.50-4.40ppm(d 1H J=1.3Hz)4.35-4.25ppm(dd 1H J=1.5Hz J=12.2Hz)4.10-4.00ppm(dd 1H J=7.0Hz J=11.7Hz)3.60-3.55ppm(dd 1H J=2.6Hz J=7.4Hz)3.50-3.45ppm(dd 1H J=4.8Hz J=7.4Hz)3.45-3.40ppm(t 1H J=2.7Hz J=2.9Hz)3.40-3.30ppm(br 3H OH)3.30-3.20ppm(s 3H OCH_3)2.30-2.20ppm(t 2H J=7.3Hz J=7.2Hz) 1.60-1.50ppm(t 2H)1.40-1.20ppm(s 24H)1.00-0.80ppm(t 3H J=6.4z J=6.9Hz).

Methyl 6-stearoyl-α-D-mannopyrannoside(2c).

R_f=0.23.m.p 48-49 ^{0}.

EIMS(m/e):429(M^+-OCH_3),411,397,368,339,285,267($C_{17}H_{35}CO^+$)(100%),
239,217,186,145,126,98,57,43.

^{1} HNMR(DMSO): 4.80-4.70ppm(d 1H J=8.1Hz)4.65-4.55ppm(dd 1H J=4.2z J=11.8Hz)4.30-4.20ppm(dd 1H J=2.2Hz J=10.2Hz)4.20-4.10ppm(dd 1H J=7.2z J=7.2Hz)3.90-3.80ppm(dd 1H J=3.4z J=3.3Hz)3.70-3.65ppm(m 1H) 3.65-3.50ppm(dd 1H J=7.09Hz J=9.3z)3.50-3.30ppm(s 3H)2.50-2.30ppm(t 2H J=7.9Hz J=7.9Hz)1.70-1.00ppm(s 28H)1.00-0.80ppm(t 3H J=6.5z J=6.9).

Methyl 6-arachidoyl-α-D-mannopyranoside(2d).

Rf=0.24m.p 50-52^0.

EIMS(m/e):457(M^+-OCH_3),439,395,377,295($C_{19}H_{39}CO^+$)(100%),277,251,236,204,163, 145,116,98,73,57,43.

^{1} HNMR(DMSO):5.00-4.90ppm(d 1H OH)4.80-4.70ppm(d 1H OH)4.70-4.60ppm(d 1H OH)4.50ppm(d 1H J=6.9)4.40-4.20ppm(dd 1H J=11.7Hz)4.10-4.00ppm(dd 1H J=6.86Hz J=11.7Hz)3.70-3.20ppm(m 7H)2.40-2.20ppm(t 2H J=7.1Hz J=7.1Hz) 1.60-1.40ppm(m 2H)1.35-1.20ppm(s 32H)0.90-0.80ppm(t 3H J=5.3Hz J=6.9Hz).

Methyl 6-undecyenoyl-β-D-galacopyranoside(3a).

Rf=0.34 m.p.99-100^0.

EIMS(m/e):361(M^++1),329(M^+-OCH_3),311,239,195,185,167($C_{11}H19CO^+$),149,125,97,60 (100%),55,41.

^{1} HNMR(DMSO):5.90-5.70ppm(m 1H)5.10-4.90ppm(m 2H),4.25-4.15ppm(dd 1H J=7.8Hz J=11.3z)4.10-4.05ppm(dd 1H J=4.4Hz J=10.3Hz)4.00-3.90ppm(d 1H J=6.4z)3.70-3.60ppm(t 1H J=4.3Hz J=7.2Hz)3.50-3.20ppm(m 9H)2.40-2.20ppm (t 2H J=7.3Hz J=7.3z)2.10-1.90ppm(dd 2H)1.60-1.50ppm(t 2H J=6.7Hz J=7.0Hz) 1.40-1.20ppm(m 10H).

Methyl 6-palimatoyl-β-D-galacopyranoside(3b).

R_f=0.41 m.p.98-100 ^{0} .

EIMS(m/e):433(M^++1),401(M^+-OCH_3),383,257,239($C_{15}H_{31}CO^+$),193,91(100%).

^{1} HNMR(DMSO):5.00-4.90ppm(d 1H OH)4.80-4.70ppm(d 1H OH)4.70-4.60ppm(d 1H OH) 4.40-4.30ppm(dd 1H J=7.8Hz J=11.9Hz)4.10-4.00ppm(dd 1H J=4.5z J=10.2Hz) 4.05-3.95ppm(d 1H J=7.5Hz) 3.70-3.50ppm(t 1H J=4.5Hz J=2.0Hz) 3.40-3.20ppm(m 6H)2.40-2.20ppm(t 2H J=7.4Hz J=7.3Hz)1.60-1.40ppm(t 2H J=7.0Hz J=7.1Hz) 1.30-1.20ppm(s 24H)0.90-0.80ppm(t 3H J=6.5Hz J=6.9Hz).

Methyl 6-stearoyl-β-D-galacopyranoside(3c)

R_f=0.45.m.p.88-89 ^{0} .

EIMS(m/e):461(M^++1),429(M^+-OCH_3),411,285,267($C_{17}H_{35}CO^+$),239,99,85,73(100%), 57,43.

^{1} HNMR(DMSO):4.30-4.15ppm(dd 1H J=7.9Hz J=11.2Hz) 4.10-4.00ppm(dd 1H J=4.4Hz J=11.2Hz)4.05-3.95ppm(d 1H J=7.6Hz)3.70-3.50ppm(t 1H J=4.2Hz J=7.3Hz)3.40-3.20ppm(m 9H)2.40-2.20ppm(t 2H J=7.3Hz J=7.4Hz)1.60-1.40ppm (m 2H)1.40-1.20ppm(s 28H)0.90-0.80ppm(t 3H J=6.5Hz J=6.9Hz).

Methyl 6-arachidoyl-β-D-galacopyranoside(3d).

R_f=0.44 m.p.88-90 ^{0}.

EIMS(m/e): 489(M^++1),457(M^+-OCH_3),439,295($C_{19}H_{39}CO^+$),99,85,71,57(100%).

^{1} HNMR(DMSO):4.30-4.25ppm(dd 1H J=7.9Hz J=11.8Hz)4.20-4.10ppm(dd 1H J=4.4Hz J=11.3Hz)4.05-4.00ppm(d 1H J=7.4Hz)3.70-3.50ppm(t 1H J=4.4Hz J=7.2Hz) 3.40-3.20ppm(m 9H)2.40-2.30ppm(t 2H J=7.3Hz J=7.1Hz)1.60-1.50ppm (m 2H) 1.40-1.30ppm(s 32H)0.90-0.80ppm(t 3H J=6.5Hz J=6.9Hz).

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