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Selective Synthesis of Glycoside Fatty Acid Esters and Their Antibacterial Structure-activity Relationship against Bacterial *Staphylococcus Aureus* and *Salmonella Agona*

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Fatty acid esters of glycosides and glucopyranosiduronides were regioselectively synthesized with tin-mediated method using dibutyltin dimethoxide as the stannylating agent, these novel esters were investigated for their antibacterial activities against bacterial *Staphylococcus Aureus* and *Salmonella Agona*, the essential structural feature as antibacterial agents was probed. Antimicrobial tests showed that some laurates of trans-ol glycosides are effective inhibitors against *S. Aureus*, while some laurates and myristates of cis-ol glycosides are moderate inhibitors against both *S. Aureus and S. Agona.* Studies on antimicrobial structure-activity relationship of sugar fatty acid esters showed that both the carbohydrate moiety and the length of fatty acid played a vital role on the antibacterial effect.

Keywords: Glycoside fatty acid esters; Tin-mediated method; Structure-activity relationship; Antibacterial.

INTRODUCTION

Sugar fatty acid esters have been reported to show antibacterial activity, particularly against gram-positive bacteria.[1] Among the first fatty acid esters of sugars reported to display antimicrobial activity were sucrose dicaprylate and sucrose monolaurate, which were shown to be active against some gram-negative and gram-positive bacteria, as well as fungi.[2,3] Fatty acid esters of sucrose have also been reported to inhibit the growth of *Vibrio parahaemolyticus*.[4] However these earlier studies were carried out using commercial preparations that contained a mixture of sugar ester compounds. Thus, it was difficult to correlate antimicrobial activity with chemical structure of sugar esters. Structure-defined carbohydrate fatty acid esters used to be chemically synthesized by direct esterification and transesterification, however an issue regarding the chemical synthesis of these esters is related to the high functionality of the carbohydrate molecule with many hydroxyl groups, which compete during the derivatization step, leading to produce mixtures of mono-, di- and polyesters;[5] Enzymatic synthesis of sugar fatty acid esters has been reported regioselective,[6-9] this novel type of fatty acid esters of carbohydrates were also reported to show antibacterial activity, for instance Devulapalle[10] and Ferrer[11] had regioselectively synthesized a series of fatty acid esters of sucrose and maltose for the use as inhibitors of the glucosyltransferases of Streptococcus sobrinus and Bacillus species. However with enzyme method in most cases only 6-OH positions of sugar moiety were acylated to produce 6-acyl isomers, which lead into limited isomers of sugar esters and hinder the elucidation of structure-activity relationship.

Organic-tin method was ever used to regioselectively introduce substituted group on the sugar moiety, 1,6-dibutylstannylene acetals are reactive intermediates which have been treated with acylating and alkylating agents to provide mono-substituted derivatives of diols or polyols with high regioselectivity.[12-16] Hence this chemical method can be used to regioselectively synthesize carbohydrate fatty acid esters, producing some sugar esters isomers which couldn't be prepared with enzyme method. The production of pure and regiochemically defined sugar fatty acid esters makes it possible to provide insights into structure/activity relationships of antibacterial effect for these compounds.

The antibacterial mechanism of action of carbohydrate esters has not yet been elucidated, but the cytoplasmic membrane is thought to be the primary site of action for fatty acid esters.[17-18] The toxic action of the esters might be due to fatty acid induced membrane disruption or due to interaction with specific processes in the bacterium. An abundance of pure carbohydrate ester isomers with varying

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structure will help to elucidate the working mechanism of these esters, this prompt us to use tin-mediated method to regioselectively prepare carbohydrate fatty acid esters.

The aim of this study was (a) to syntheses series of glycoside fatty acid esters using tin-mediated method, and (b) to address the antimicrobial structure-activity relationships of this novel type of carbohydrate fatty acid esters, meanwhile the regioselectivity of tin-mediated method on acylation of fatty acid and glycosides was also probed.

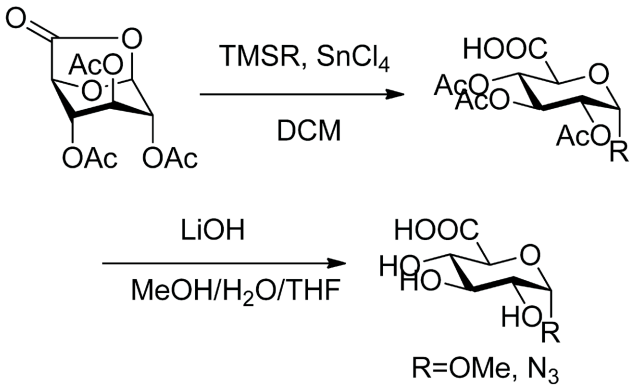
RESULTS AND DISCUSSION

Synthesis of fatty acid esters of glycosides

To probe the antimicrobial structure-activity relationship of sugar fatty acid esters, various sugar esters with diverse structure are needed to be synthesized. Carbohydrates, which will be selectively acylated with tin-mediated method, have to meet certain structural requirement for region-selective substitution, hence some structurally similar cis-ol and trans-ol glycosides were chosen to be selectively acylated to give fatty acid esters. Beside commercially available glycosides, α-glucuronides were also tried as sugar substrates in order to probe the sugar substrate scope suitable for tin-mediated method. Stanylene acetal method insofar was only applied into the sugar substrates without active groups, whether this method can work on sugar substrates bearing active COOH groups is an issue of interest. However, the α configuration of glucuronide, which is possibly to be regioselectively acylated with stannylene method, need to be stereoselectively synthesized from glucuronic acid. Many methods were documented to convert glucuronic acid into α-D-glucuronides, among reported methods the one by TMSR mediated ring opening of 1,6-anhydro sugars is rather effective with high selectivity,[19-21] as shown in Scheme 1. With this method two substrates methyl α-D-glucopyranosiduronide and azido α-D-gluco pyranosiduronide were prepared.

Tin-mediated method has proved to introduce substituted group on the sugar moiety as benzoyl, acetyl group with high regioselectivity. It is of interest whether this tin-mediated acylation is suitable for long-chained acylating agents. In this work, different length of fatty acids, from octanoic acid (C8) to stearic acid (C18), were tested to be introduced into glycosides and α-D-glucopyranosiduronic acids with stannylene acetal method. Dibutyltin dimethoxide (DBDM), instead of more common dibutyltin oxide (DBO), was used as stannylating agent. DBDM was documented to show rapid formation of dibutylstannylene

Scheme 1 Stereoselective synthesis of methyl(azide) α-D-glucopyranosiduronic acid via 1, 6-lactone



acetals with poly-hydroxyl groups at room temperature and easier handle of workup for acylation and alkylation reactions.[22-24]

The factors governing regioselectivity of this reaction were intensively investigated. For reaction solvent, dioxane was found to be optimal one among various solvents tested, in which regioselective reaction can proceed smoothly and judged with HPLC. Surprisingly, the regioselectivity was not observed by the replacement of dioxane with toulene or acetonitrile, etc. The effect of temperature was also probed on regioselectivity of acylation reaction. It was found that the selective reaction preferred to occur at 0-5 °C. Long-chained fatty acid were selectively introduced into glycoside and glucuronide on optimized condition giving corresponding esters.

Using the optimal conditions mentioned above, a series of fatty acid esters of glycosides and glucopyranosiduronides were prepared and separated with flash chromatography and preparative HPLC method. The synthesized esters were methyl 2-O-acyl-α-D-glucopyranoides (1-6), methyl 2-O-acyl-α-D-mannopyranosides (7-12), methyl 3-O-acyl-α-D-manopyranosides (13-18), methyl 3-O-acyl-β-D-galacto-pyranosides (19-24), methyl 2-O-acyl-α-D-glucuronic acids (25-27) and azido 2-O-acyl-α-D-glucuronic acids (28-30) as shown in Figure 1. The yields of corresponding esters are listed in Table 1.

Tin-mediated regioselective acylation of glycosides and glucopyranosiduronides

The tin-mediated regioselective acylation of various glycosides and glucopyranosiduronides with fatty acid chloride was probed. In most cases, the satisfactory regioselectivity was observed on optimized conditions ex-

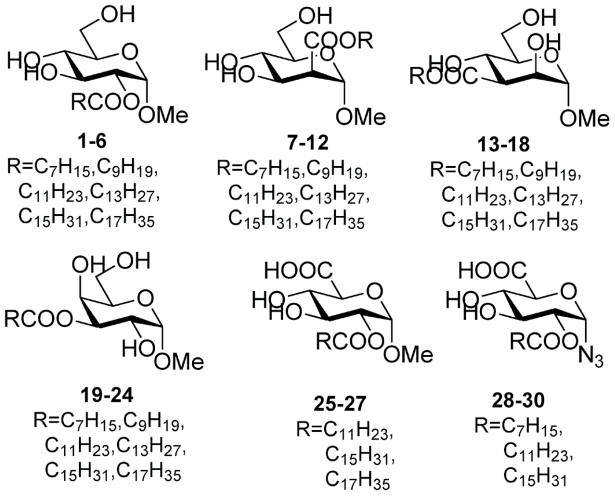


Fig. 1. Structures of carbohydrate fatty acid ester derivatives synthesized with tin-mediated method.

Table 1. The given yields of glycoside fatty acid esters on optimized conditions

Compounds	Yields (%)		Reaction conditions
Methyl 2-acyl-α-D-glucopyranoside	octanoyl (**1**)	73	Methyl α-D-gluco pyranoside: DBDM: fatty acid chloride = 1:1.1:1.1 Solvent: dioxane Temp.: 5 °C
	decanoyl (**2**)	63	
	lauoryl (**3**)	72	
	myristoyl (**4**)	81	
	palmitoyl (**5**)	75	
	stearoyl (**6**)	78	
Methyl 2-acyl-α-D-mannopyranoside	octanoyl (**7**)	33	Methyl α-D-manno pyranoside: DBDM: fatty acid chloride = 1:1.1:1.1 Solvent: dioxane Temp.: 5 °C
	decanoyl (**8**)	30	
	lauoryl (**9**)	31	
	myristoyl (**10**)	31	
	palmitoyl (**11**)	29	
	stearoyl (**12**)	28	
Methyl 3-acyl-α-D-mannopyranoside	octanoyl (**13**)	32	
	decanoyl (**14**)	27	
	lauoryl (**15**)	30	
	myristoyl (**16**)	32	
	palmitoyl (**17**)	28	
	stearoyl (**18**)	28	
Methyl 3-acyl-β-D-galactopyranoside	octanoyl (**19**)	75	Methyl β-D-galacto pyranoside: DBDM: fatty acid chloride = 1:1.1:1.1 Solvent: dioxane Temp.: 25 °C
	decanoyl (**20**)	67	
	lauoryl (**21**)	74	
	myristoyl (**22**)	70	
	palmitoyl (**23**)	74	
	stearoyl (**24**)	70	
Methyl 2-acyl-α-D-glucuronic acid	lauoryl (**25**)	95	The same with above
	palmitoyl (**26**)	95	
	stearoyl (**27**)	96	
Azido 2-acyl-α-D-glucuronic acid	octanoyl (**28**)	85	The same with above
	lauoryl (**29**)	82	
	palmitoyl (**30**)	87	

cept for methyl α-D-mannopyranoside, in which an isomer mixture of 2-O-acyl-α-D-mannopyranoside and methyl 3-O-acyl-α-D-mannopyranoside with ratio of 1:1 was observed. The results showed that regioselective acylation with long-chained fatty acid are nearly the same as those of benzoylations; the long chained fatty acids seem not hinder the selectivity of dibutylstannylene acetals formed in the reaction system.

The origin of regioselectivity for tin-mediated acylation has been attributed to the inherent structure of the pyranoside, the selectivity rules governing benzoylation of glycoside seem still be applied into the acylation of fatty acid. For cis-ol system glycosides (CSG, at least one pair of cis-diol on carbohydrate moiety), the hydroxyl group at equatorial position has advantage of being acylated. For example, methyl β-D-galactopyranoside acylation happened exclusively on 3-OH position. For trans-ol system glycosides (TSG, all hydroxyl groups in trans-position), regioselectivity was observed with the hydroxyl group adjacent to the axial substituent if one adjacent substituent is equatorial and one is axial. Herein acylation exclusively happened at 2-OH position of methyl α-D-glucopyranoside, methyl α-D-glucopyranosiduronic acid and azido α-D-glucopyranosiduronic acid. The results suggest that the stannylene complex dimer of β-D-galactopyranoside, α-D-glucopyranoside, and α-D-glucuronic acid is 1,1 or 2,2-dimer during the dimerization of 2,2-dibutyl-1,3,2-dioxastannolanes formed from vicinal-diols of pyranoside rings,[25] which account for excellent selectivity; while for methyl α-D-mannopyranoside a 1,2-dimer is formed, the result of 1,2-dimerization is to activate both 2-OH and 3-OH of methyl α-D-manopyranoside, substitution occurs equally on the 2 and 3 position, which account for the formation of mixture of 2,3 isomers at a ration of 1:1 (Fig. 2).

Antibacterial structure-activity relationship of sugar fatty acid ester

These regioselectively synthesized fatty acid esters were screened as antibacterial agents against a gram-positive organism *Staphylococcus aureus* and a gram-negative organism *Salmonella agona* of interest to the food industry. The bacteria were grown as described in the experimental section and were added to the sugar esters solution to a final concentration of 100 ppm. The effect of configuration of glycoside fatty acid esters on the antibacterial activity was investigated; the esters investigated were classified into

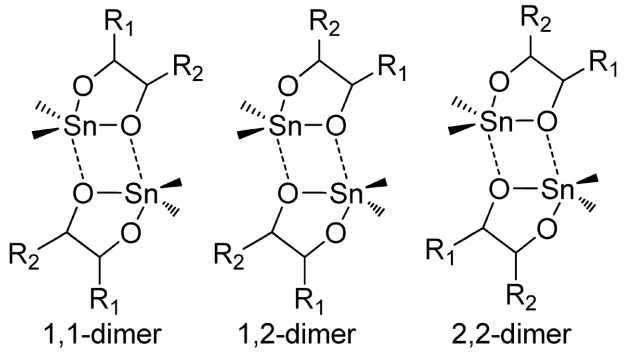


Fig. 2. The structure of dimers of the dialkylstannylene acetal of 1,2-diol system.

two classes: cis-ol system and trans-ol system glycosides fatty acid esters. Initially how the chain length of esters influence their antimicrobial activity was studied.

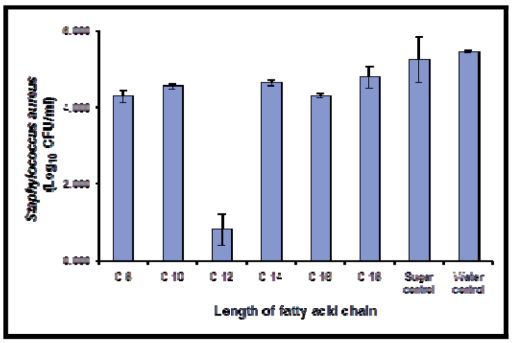
Influence of chain length of fatty acid moiety of two types of glycoside esters on antibacterial activity

Figure 3 showed the results of screening of fatty acid esters of trans-ol glycosides (methyl α-D-glucopyranoside and methyl α-D-glucuronic acid as examples) against *Staphylococcus Aureus* and *Salmonella Agona.*

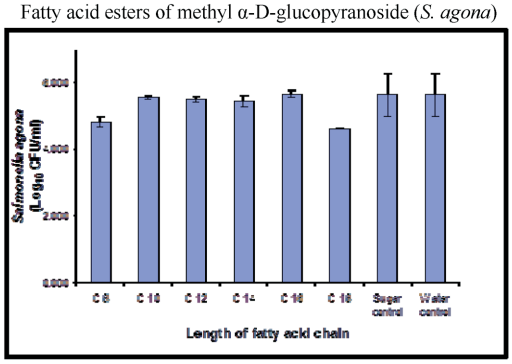
Antibacterial screening studies showed that the length of fatty acid chain played a vital role on the antibacterial effect for TSG esters, the chain length of 12 carbons being optimal, it is observed from Fig. 3 that the lauroyl derivatives of both methyl α-D-glucopyranoside and methyl α-D-glucuronic acid, had a specific and potent antibacterial effect against *Staphylococcus aureus*. The population of S. aureus was reduced from 5.445 (water control) to 0.814 Log10 CFU/m for glucopyranoside laurate, and the population of S. aureus was reduced from 5.263 (water control) to 1.150 Log10 CFU/ml for methyl 2-lauroyl-α-D-glucuronic acid. However, the two same esters didn't show any sign to inhibit the growth of gram-negative bacterial *Salmonella Agona*.

Figure 4 showed the results of screening of fatty acid esters of cis-ol system glycosides (methyl α-D-mannopyranoside and methyl β-D-galactopyranoside as examples) against *Staphylococcus Aureus* and *Salmonella Agona*.

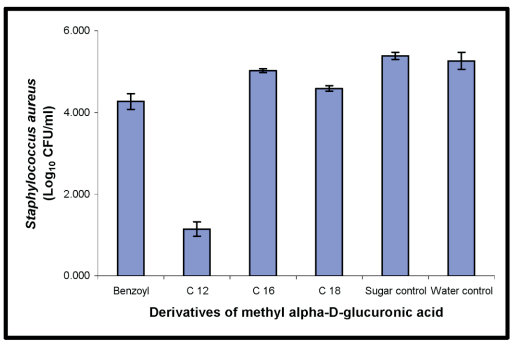
For CSG esters antibacterial screening studies showed that the length of fatty acid chain played a marked role on the antibacterial effect as well. It appears that the chain length of the fatty acid moiety is critical with a chain length between 12-14 carbons being optimal. The laurate and myristate for methyl α-D-mannopyranoside and me-



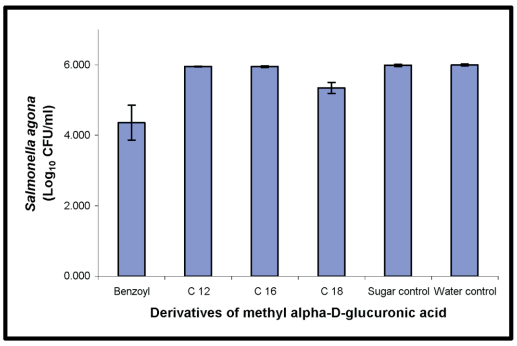
Fatty acid esters of methyl α-D-glucopyranoside (*S. agona*)



Fatty acid esters of methyl α-D-glucopyranoside (*S. aureus*)

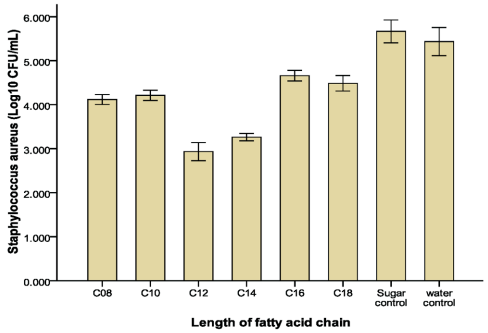


Fatty acid esters of methyl α-D-glucuronic acid (*S. aureus*)

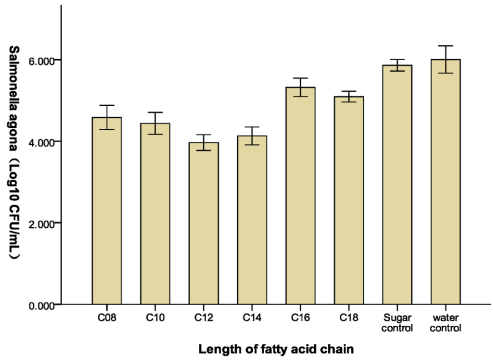


Fatty acid esters of methyl α-D-glucuronic acid (*S. agona*)

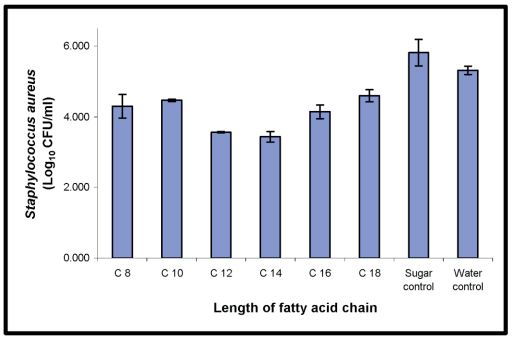
Fig. 3. Influence of chain length of fatty acid esters of methyl α-D-glucopyranoside and methyl α-D-glucuronic acid on the growth of *Staphylococcus aureus* (left) and *Salmonella agona* (right) in culture.



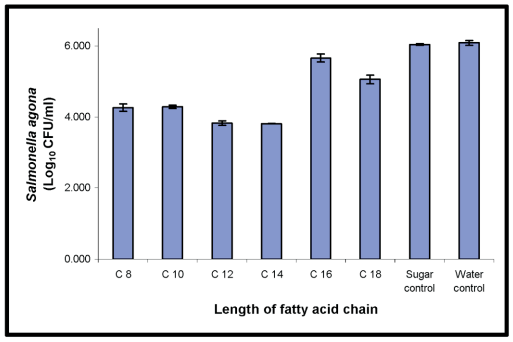
Fatty acid esters of methyl α-D-mannopyranoside(*S. aureus*)



Fatty acid esters of methyl α-D-mannopyranoside(S. agona)



Fatty acid esters of methyl β-D-galactopyranoside(*S. aureus*)



Fatty acid esters of methyl β-D-galactopyranoside(*S. agona*)

Fig. 4. Influence of chain length of fatty acid esters of methyl α-D-mannopyranoside and methyl β-D-galactopyranoside on the growth of *Staphylococcus aureus* and *Salmonella agona* in culture.

thyl β-D-galactopyranoside are moderate inhibitors against *S. Aureus*. The population of *S. aureus* was reduced from 5.348 (water control) to 3.319 (C14) and 2.924 Log10 CFU/ml (C12) for myristate and laurate of mannopyranoside, and the population of *S. aureus* was reduced from 5.322 (water control) to 3.441 (C14) and 3.563 Log10 CFU/ml (C12) for galactopyranoside myristate and laurate. Interestingly it is the same two esters that are moderate effective aginst S. Agona as well. The population of *S. agona* was reduced from 5.964 (water control) to 4.113 (1c) and 3.911 Log10 CFU/ml for myristate and laurate of mannopyranoside, the population of *S. agona* was reduced from 6.094 (water control) to 3.813 and 3.830 Log10 CFU/ml for myristate and laurate of galactopyranoside.

Influence of carbohydrate moiety of sugar esters on antibacterial activity

Antibacterial screening showed that some lauroyl esters of sugar had a potent antibacterial effect against *Staphylococcus aureus*, in order to investigate the relationship between the structure of carbohydrate moiety and antimicrobial activity, the chain length of fatty acid moiety is confined to 12 carbons, their corresponding esters as antibacterial agents against *Staphylococcus aureus* and *Salmonella agona* were screened as shown in Fig. 5.

The results showed that the structure of the carbohydrate moiety is closely correlated with affected antimicrobial activity of carbohydrate esters, the laurates of CSG (galactopyranoside and mannopyranoside) were less effective than that of TSG (glucopyranoside and glucuronic acid derivative) as an inhibitor of the growth of *S. aureus*. The population of *S. aureus* was reduced from 5.348 (water control) to a level appropriately 3 Log10 CFU/ml for CSG esters, while for TSG esters encouragingly reduced to a level appropriately 1Log10 CFU/ml, that means that the trans configuration of hydroxyl groups of carbohydrate moiety is a key factor for the esters' inhibition of microbiology, however all these laurates of glycosides were not so effective to inhibit the growth of *S. agon* when compared to *S. Aureus*. It is of interest that the alkyl group on anomeric position of carbohydrate moiety also takes a role in the inhibition of bacteria, when methyl group is replaced with azido group for 2-O-acyl-α-D-glucuronic acids, the azido derivative had an better antibacterial effect against *Salmonella agona* than methyl derivative.

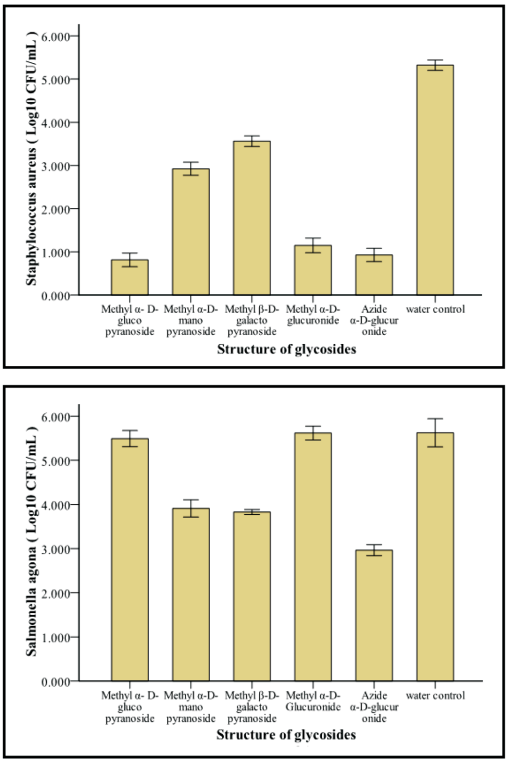


Fig. 5. Influence of glycoside configuration of lauroyl esters on the growth of *S. aureus* (above) and *S. agona* (below) in culture.

EXPERIMENTAL

Materials and Instrumentation: ^{1}H chemical shifts in CD_3OD were referenced to CHD_2OD (3.30 ppm); constants are reported in hertz. FTIR spectra were recorded with a Nicolet FTIR 3000 using KBr discs, as specified. Melting points were measured on a STUART melting point apparatus. Low and high-resolution mass spectra were measured on electrospray mass spectrometry in ES negative mode unless otherwise indicated. Flash column chromatography was carried out with silica gel 60 (0.040-0.630 mm, E. Merck) and using a solvent mixture system correlated with TLC mobility. DBDM, DBO, glycopyranosides, octanoyl chloride, decanoyl chloride, lauroyl chloride, myristoyl chloride, palmitoyl chloride, stearoyl chloride, were purchased from Sigma-Aldrich.

Stereoselective Synthesis of Methyl α-D-glucuronic Acid and Azido α-D-glucuronic Acid: Lactone (3.02 g, 10 mmol), TMSOMe (2.6 g, 25 mmol, 2.5 equiv.) and $SnCl_4$ (4.68 mL, 40 mmol, 4 equiv.) were added into anhydrous dichloromethane (40 ml) under N_2 and the reaction mixture was stirred overnight. The mixture was diluted with dichloromethane and the solution was vigorously stirred for a further 30-40 minutes in the presence of an equal volume of saturated $NaHCO_3$. A white emulsion was formed and the organic and aqueous layers were easily separated after filtering through filter paper. Following removal of the organic solvent, a white powder was obtained (2.4 g, 7.19 mmol, 72%). Protected methyl α-D-glucuronic acid (2.4 g, 7.18 mmol) was suspended in 0.1 N LiOH in MeOH/H2O/THF (2.5/1.0/0.5, 10 ml) at 0 °C (ice bath) and stirred for 2 h. The solution was diluted with water and acidified to pH 2 using Amberlite IR-120. Removal of the solvents gave methyl α-D-glucuroinc acid (1.3 g, 6.25 mmol, 87%). Azido α-D-glucuroinc acid was prepared with the same method mentioned above and overall yield was 59.8 from lactone.

Selective Synthesis of Sugar Fatty Acid Esters: D-glycopyranoside or glucopyranosiduronide (5 mmol) was dissolved in dioxane or other solvents (40 mL). DBDM (1.47 mL, 5.5 mmol) was added into the solution, causing effervescence. The reaction mixture was kept at r.t. and a solution of fatty acid chloride in dioxane (5.5 mmol, 10 mL) was added dropwise over one hour. The reaction was monitored using TLC and terminated when all the starting material had been converted (24 h). The mixture was evaporated under vacuum to give syrup. This was fractionated by flash chromatography using a solvent mixture of chloroform and methanol to give the desired monoester.

HPLC Method Development for Analysis and Separation of Fatty Acid Ester Position Isomers: Thin-layer (TLC), gas-liquid (GLC) and high performance liquid chromatographic (HPLC) methods have been developed to identify and separate isomers of sucrose fatty acid esters.[26] However when these same methods are applied to analysis of the positional isomers of fatty acid esters of D-glycoside satisfactory separation of isomers couldn't be achieved. In order to examine the regioselectivity of esterification and separate monoester isomers of D-glycoside a variety of solvent combinations were probed to determine the suitable system, and a three solvent system (methanol:acetonitrile:water = 70:20:10) was eventually found to separate completely these isomers.

Bacterial growth on agar plates and inhibition assay

Preparation of Test Organisms: Staphylococcus aureus stock cultures were maintained in 20% glycerol at -20 °C. 1 ml of thawed culture was transferred to 30 ml of BHI and incubated at 37 °C for 24 hours. 1 ml of the 24 hour culture was transferred into 100 ml BHI and incubated at 37 °C for 14 hours. 50 ml of the 14 hour culture was centrifuged at 4800 rpm for 10 minutes. The supernatant was discarded and the pellet washed and suspended in 9 ml of Maximum Recovery Diluent (Oxoid, CM733, MRD). The culture was centrifuged again at 4800 rpm for 5 minutes and the pellet suspended in 9 ml BHI. This culture was diluted 1: 100

to yield a working culture. Salmonella agona was prepared using the same method. All bacterial counts were expressed in log Colony Forming Units per ml (log CFU/ml).

Addition of bacteria to Sugar Ester Solution: 1 ml aliquots of each bacterial suspension were transferred into 10 ml of sugar ester solution to yield a final concentration of 100 or 150 μg/ml (ppm). Each tube was incubated at 37 °C for 6 hours. Each trial was carried out in duplicate.

Microbiological Analysis: Each bacterial suspension and sugar ester solution mixture was serially diluted and enumerated in duplicate on Plate Count Agar (Oxoid, CM325, PCA). Plates were incubated at 37 °C for 24 hours and plates with appropriate levels of bacteria were selected for counting.

CONCLUSIONS

Stannylene acetal method can be used to synthesize fatty acid esters of glycoside with high regioselectivity, the sugar substrate can be extended into those containing active group as COOH, the general selective rule of stannylene acetal method still govern the acylation of fatty acid on glycosides. For the antibacterial activity of glycoside fatty acid esters, the essential structural features as antibacterial agents can be partly defined from this study. It appears that the chain length of the fatty acid moiety is critical with a chain length between 12-14 carbons being optimal. Fatty acid esters of TSG are more dependent on combining a suitable length of fatty acid to produce desired antibacterial effect than esters of CSG. For sugar moiety, the configuration of hydroxyl group in the carbohydrate moiety markedly affects their antibacterial activity, sugar esters of trans configuration are more effective to inhibit the growth of bacteria than that of cis configuration, subsequently further work is needed to define the precise structural features of carbohydrate fatty acid esters crucial to the antibacterial activities observed in this work.

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