Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 11, pp. 2163-2178, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00295-9

Dibutylstannylene Acetals: Useful Intermediates for the Regioselective Sulfation of Glycosides.

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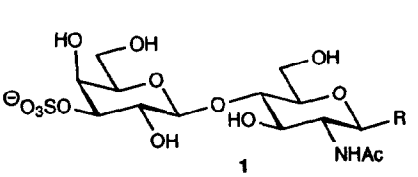
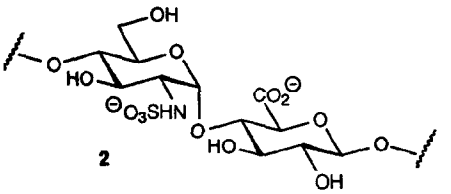
Abstract: Sulfated mono- and disaccharides were synthesised by a novel sulfation method *via* regioselective activation of the saccharides to their dibutyltin stannylene acetals, followed by treatment with sulfur trioxide-trimethylamine. This methodology was applied to the synthesis of 3'-sulfated lactosides **15** and **23**, galactosylceramide sulfatide **3** and 2'-sulfated maltosides **30**, **32** and **34**.

In recent years, oligosaccharides and glycoconjugates containing sulfates and aminosulfonates have been isolated and characterised, and have been shown to play important roles in biological recognition processes. For example, 3'-*O*-sulfo-N-acetyllactosaminide **1** is a partial structure of the 3'-*O*-sulfo-Lewis^x antigen which is recognised by E-selectins during the inflammatory response.[1] Compound **1** itself has been shown to be useful for detecting high levels of serum α-1,3-L-fucosyltransferase in ovarian cancer patients, since it is a selective substrate for this enzyme.[2] Disaccharide **2** is a partial structure in heparan sulfate, which has recently been identified to be part of a specific basic fibroblast growth factor (bFGF) binding sequence, that participates in activation of bFGF and hence regulation of cell growth.[3] Galactosylceramide sulfatide **3** is a mammalian glycolipid, which has been isolated from spinal cord.[4]



1



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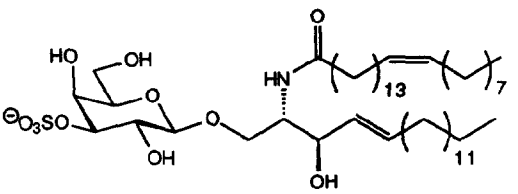
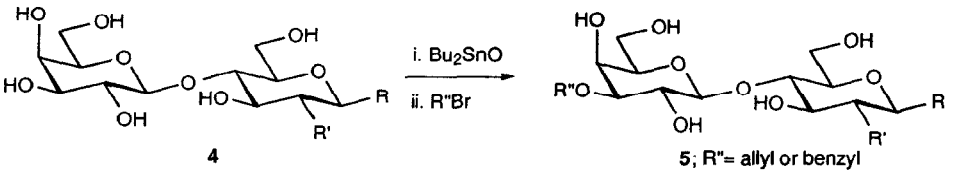


3

The synthesis of natural sulfated oligosaccharides and of analogues containing various modifications is not trivial since it requires extensive protection and deprotections steps. For example, in the synthesis of structures related to **2**, at least three orthogonal protecting groups per monosaccharide unit have to be employed

in synthesis: one for protecting the C-4 hydroxyl group, which needs to be selectively free for coupling; a second protecting group for those amino/hydroxyl groups which need to be sulfated during synthesis; and a third protecting group for those hydroxyl groups that remain free in the final product.[5] As part of an ongoing programme, we have been interested in developing synthetic methods for complex carbohydrates which minimise the use of protecting groups by the use of highly regioselective reagents. This has led us to develop a method of regioselective sulfation using the well known dibutylstannylene acetals of glycosides as activated intermediates.[6]

Dibutyltin oxide is known to form five membered (sometimes six or seven membered) cyclic dibutylstannylene acetals with saccharides, preferably with *cis* diol configurations.[7,8] In these complexes, the nucleophilicity of the equatorial hydroxyl group is enhanced[9] towards acylation, alkylation, tosylation or silylation.[8,10] For example, the unprotected β-lactoside **4** was converted exclusively to the 3'-*O*-derivative **5** *via* the reaction of its 3',4'-dibutylstannylene acetal with allyl or benzyl bromide (scheme 1).[11] In the case of silylation, the reversible migration of the stannylene acetal from the 3',4' positions to either the 4',6' or ring oxygen, 6' positions led to the 6'-*O*-derivative.[10] When using α-glycosides containing no *cis* diols, or when the *cis* diols are protected, the dibutylstannylene acetal can complex between the 2 position and the anomeric oxygen to give the 2-*O*-derivative by reaction with an electrophile.[12]

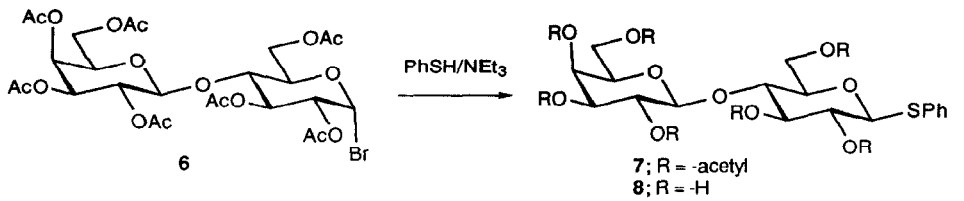


4 **5**; R"= allyl or benzyl

(R = -OMe, -Oallyl, -OEtSiMe3; R' = -OH, -NHAc)

Scheme 1

Based on these reports, the regioselective sulfation of phenyl thio-β-lactoside **8** was initially studied, as it is easily obtained from bromolactose heptaacetate and thiophenol,[13] followed by standard deacetylation (scheme 2).



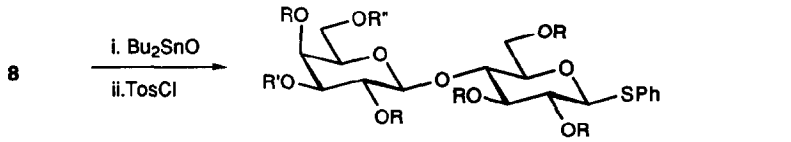
6

7; R = -acetyl
8; R = -H

Scheme 2

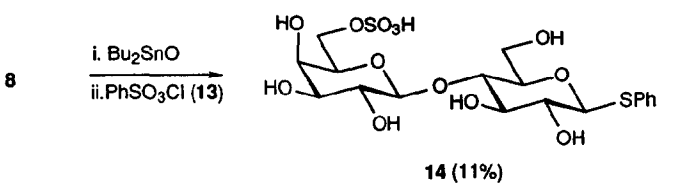
The stannylene acetal complex was prepared by stirring **8** with dibutyltin oxide in refluxing methanol followed by removal of the solvent *in vacuo*. The initial aim was to introduce the sulfate in a protected form, such as the phenylsulfate group, which had already been used with saccharides.[14] Because of its structural similarity to phenylchlorosulfate, reactions with tosylchloride were first investigated, in order to establish that

tosylation has the same regioselectivity as alkylation. Thus, the dry dibutylstannylene acetal prepared from **8** was treated with 15 equivalents of tosyl chloride and 0.5 equivalent of tetrabutyl ammonium bromide in refluxing THF. Bromide anions are known to activate the reaction by nucleophilic substitution on the tin complex.[15] The reaction occurred readily forming the 3'-*O*-tosyl derivative **9** as the major isolated product (~75%), and the 3',6'-di-*O*-tosyl lactoside **11** as the minor product (15% yield, scheme 3). The formation of **11** could be due to initial tosylation at the 3' position with migration of the stannylene acetal to activate the 6' position towards a second tosylation. The ^{1}H NMR spectrum of **9** and **11** confirmed the presence of one and two tosyl groups respectively and the regioselectivity of tosylation was confirmed by the downfield shift of the 3'-H in **9** and of 3'-H and 6'-H in compound **11**. Unambiguous characterisation of **9** and **11** was possible after peracetylation to **10** and **12** respectively. Thus, tosylation seemed to have occurred with similar regioselectivity as reported for benzylation and allylation.[11]



Scheme 3

These results encouraged us to look at the reaction of phenylchlorosulfate **13**[14a] with the stannylene acetal of **8**. However, analysis of the reaction mixture by thin layer chromatography revealed that the reaction had not gone to completion and that a mixture of products had been formed. Only compound **14** containing a 6'-*O*-sulfate group was isolated from this mixture in 11% yield (scheme 4). **14** had presumably been formed by decomposition of the corresponding 6'-*O*- phenylsulfate. Thus it appears that phenylchlorosulfate is less reactive and less selective when compared to tosylchloride. The reaction was repeated with the more reactive *p*-nitrophenylchlorosulfate, again with little success.

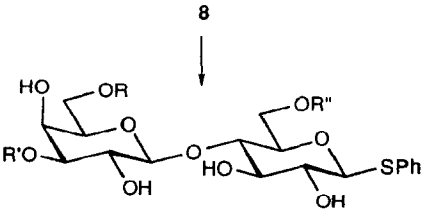


Scheme 4

As a more reactive sulfation reagent, and one which should yield stable products, $Me_3N.SO_3$ was chosen to react with the dibutylstannylene acetal of **8**. This reaction proved to be unexpectedly successful. Thus treatment with two equivalents of $Me_3N.SO_3$ in dioxane at room temperature for 30 hours resulted in the conversion of the dibutylstannylene acetal of **8** to the 3'-*O*-sulfo-lactoside **15** (76%) and the 3',6'-di-*O*-sulfo-lactoside **16** (10%), both isolated as their sodium salts (scheme 5). The selectivity is the same as that observed

with allyl, benzyl or tosyl halide and would be expected to proceed *via* the same 3',4' stannylene acetal intermediate. The presence of a sulfate group can be observed by NMR spectroscopy in that it causes a downfield shift of 3'-H and 4'-H to 4.01 and 3.87-3.89 ppm respectively[16] in compound **15** compared to **8**, and also of 6'-H in compound **16**. The structure of **15** was also confirmed by independent synthesis *via* an alternative conventional 5 step route[17] from **8**, which led to a product with identical spectroscopic data.

Since $Me_3N.SO_3$ can react with hydroxyl groups without the need for an added base, we investigated the reaction of **8** with $Me_3N.SO_3$ to establish that the observed selectivity was indeed due to activation by the tin complex. Firstly, no reaction was observed when the lactoside **8** was just stirred under identical conditions (in dioxane) with $Me_3N.SO_3$, possibly due to the poor solubility of **8** in this solvent. However, sulfation proceeded when a solution of **8** in DMF was treated with two equivalents of $Me_3N.SO_3$ (scheme 5). Contrary to the previous reaction a mixture of at least three products **14**, **17** and **18** besides starting material was formed, notably none of them containing a sulfate at the 3' position. This confirmed that activation by dibutyltin oxide was necessary for the observed regioselectivity of sulfation.



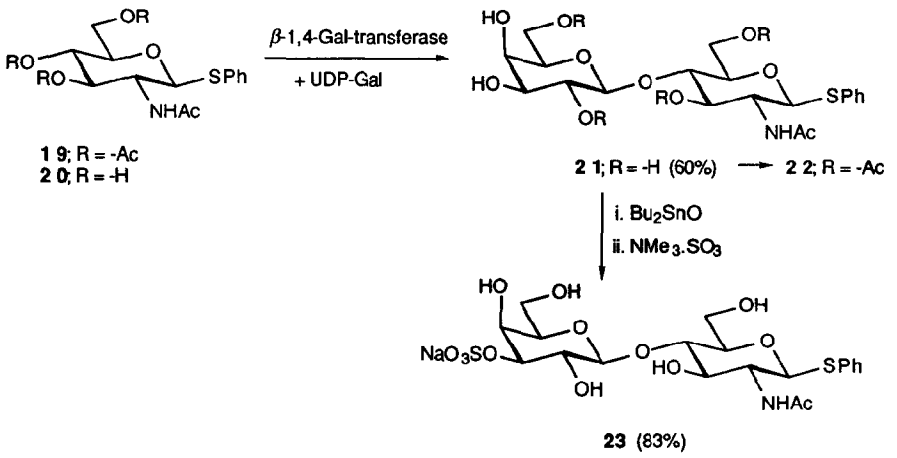
	R	R'	R"
14	$-SO_3H$	-H	-H
15	-H	$-SO_3Na$	-H
16	$-SO_3Na$	$-SO_3Na$	-H
17	-H	-H	$-SO_3H$
18	$-SO_3H$	-H	$-SO_3H$

reaction conditions	isolated compounds (yields)					
	8	**15**	**16**	**14**	**17**	**18**
i) Bu_2SnO, MeOH ii) $Me_3N.SO_3$ dioxane	-	76%	10%	-	-	-
$Me_3N.SO_3$, DMF	13%	-	-	17%	9%	15%

Scheme 5

This methodology of selective sulfation was applied to the synthesis of sulfated N-acetyl lactosaminide **23**, the thiophenyl glycoside of **1**. Thiophenyl N-acetyllactosaminide **21** is not commercially available and was prepared by enzymatic galactosylation of **20** using β-1,4-galactosyltransferase from bovine milk. It is interesting to note that it has previously been reported that **20** is not a substrate for this enzyme[18] but in our hands gave **21** in good isolated yield (60%) using previously described procedures (scheme 6).[19] Our results might be due to using a higher concentration of enzyme and acceptor (1U/ml; 40 mM) as compared to the previous study (40 mU/ml; 25 mM). The 1,4-linkage in **21** was confirmed by NMR studies after acetylation. Treatment of **21** with acetic anhydride/pyridine at room temperature gave, after 45h, compound **22** which surprisingly contained free 3' and 4' hydroxyl groups. Nevertheless, the relevant ring protons in **22** showed a suitable spread of NMR signals to make NOE experiments possible. Upon acetylation of **21** to **22**, the 4-H signal was not shifted downfield and irradiation of 1'-H and 6'-Hb at 4.38 ppm caused 4.7% enhancement of

the 4-H signal and as expected of 5'-H, 3'-H (7%) and 6'-Ha (8%) confirming the existence of a 1,4-linkage in **22**.



Scheme 6

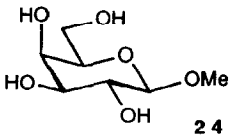
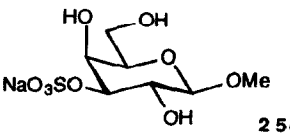
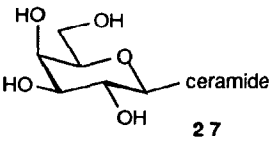
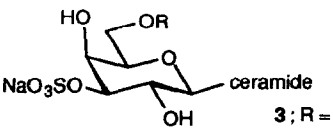
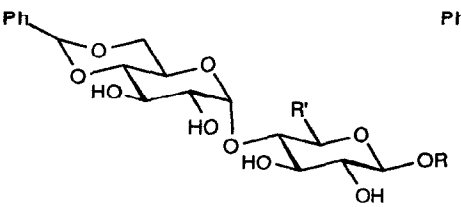
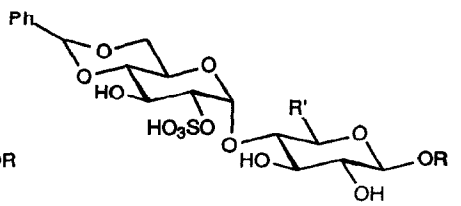
Sulfation of the dibutylstannylene acetal of **21** in THF with $Me_3N.SO_3$ gave exclusively the 3'-*O*-sulfated compound **23** in 83% isolated yield (scheme 6). Interestingly, no formation of other sideproducts, as found for the sulfation of the corresponding lactoside **8**, was observed. NMR and high resolution mass spectrometry data were in agreement with the 3' sulfated compound **23**. The synthesis of **23** illustrates a particularly useful feature of the present sulfation method in that it can easily be combined with enzymatic methodologies.

The present sulfation method was further applied to the synthesis of various mono- and disaccharides as summarized in table 1. Sulfation of the methyl β-galactoside **24** was very selective giving **25** in 93% isolated yield. The structure was confirmed by NMR spectroscopy (COSY) on the peracetylated derivative **26**. The method is also applicable to the synthesis of glycolipids such as the sodium salt of **3**. Thus, galactosylceramide **27** was selectively sulfated in 97% isolated yield with a trace of the 3',6'-disulfated sideproduct **28** being formed. It is interesting to note that the allylic hydroxyl group on the ceramide did not react.

Finally, the selective sulfation of maltosides such as **29**[20], **31** and **33**[21] was investigated as part of an ongoing programme concerning the synthesis of heparan sulfate fragments such as **2**.[22] Selective sulfation at the desired 2' position of these maltosides to **30**, **32** and **34** respectively was indeed achieved in medium to good yields (table 1).

In conclusion, we have shown that the activation of selected hydroxyl groups in unprotected or partially protected saccharides by dibutyltin oxide can lead to selectively sulfated saccharides in good to excellent yields. We have shown that this methodology can be applied to the synthesis of a variety of natural products. It will be interesting to see if this method can be extended to the sulfation of other hydroxyl groups, in particular for the synthesis of 6-sulfated saccharides.[23] As part of our synthetic work on heparan sulfate fragments, we are interested in applying the method to the sulfation of higher saccharides.

Table 1: Regioselective Sulfation of Various Saccharides Using the Present Methodology

STARTING MATERIAL	PRODUCT (YIELD)
 **2 4**	 **2 5** (93%)
 **2 7**	 **3** ; R = -H (97%) **2 8**; R = -SO_3Na (trace)
	
2 9; R = -Bn, R' = - CH_2OH	**3 0**; R = -Bn, R' = - CH_2OH (87%)
3 1; R = -allyl, R' = - CO_2*tert*-Bu	**3 2**; R = -allyl, R' = - CO_2*tert*-Bu (54%)
3 3; R = -allyl, R' = - CH_2OSi*tert*-$BuMe_2$	**3 4**; R = -allyl, R' = - CH_2OSi*tert*-$BuMe_2$ (56%)

Acknowledgements: We thank Mrs. E. McGuinness and Dr. T. Claridge for NMR measurements, Dr. C. Robinson and the SERC Mass Spectrometry Service Centre (Swansea) for MS measurements. This work was supported by the BBSRC and the DTI as a LINK grant in collaboration with Genzyme Ltd. NJD was supported by a QUOTA studentship from the SERC and MP by an earmarked studentship from the BBSRC.

Experimental

General - Reactions were carried out in solvents distilled from standard drying agents; thin layer chromatography was performed on aluminium backed silica gel sheets $60F_{254}$ (Merck, layer thickness 0.2 mm); the components were detected by heating the TLC after spraying with a solution of 5% sulfuric acid-5% anisaldehyde in ethanol; silica gel C60 (Merck 40-60 μm) was used for flash chromatography; NMR spectra were recorded on a Bruker AM-500 MHz, Varian Gemini 200 MHz or Bruker AM 200 MHz spectrometers using solvents as stated; coupling constants *J* are in Herz; I.R. spectra were recorded on a Perkin-Elmer 1750 spectrometer and optical rotations on a Perkin-Elmer 241 polarimeter; mass spectrometry was carried out on VG Analytical Ltd, ZABIF or BIO-Q mass spectrometers using chemical impact (CI/NH_3), ammonia desorption chemical ionisation (DCI/NH_3), positive argon fast atom bombardment (FAB) and negative electrospray (ES^-) as indicated; high resolution mass spectra were recorded on a VGAutospecEQ spectrometer (FAB^-), Brucker FTICR using matrix assisted laser desorption ionisation (MALDI) or liquid secondary ionisation mass spectrometry (LSIMS) or by the EPSRC mass spectrometry service centre at Swansea; uridine 5'-diphospho-glucose (UDP-glucose), uridine 5'-diphospho-glucose 4-epimerase (EC 5.1.3.2), β-1,4-galactosyltransferase from bovine milk (EC 2.4.1.22) and galactocerebroside (Type II, contains primarily nervonic acid) were purchased from Sigma; calf intestinal alkaline phosphatase (CIAP) (EC 3.1.3.1) and bovine serum albumin (BSA) were obtained from Boehringer Mannheim.

Phenyl 2,3,6-*tri*-O-*acetyl*-4-O-(2',3',4',6'-*tetra*-O-*acetyl*-β-D-*galactopyranosyl*)-1-*deoxy*-1-*thio*-β-D-*gluco pyranoside* **7**

A solution of heptaacetobromo-α-D-lactose (3.70 g, 5.29 mmol) in CH_3CN (20 ml) was stirred with thiophenol (0.652 ml, 6.35 mmol) and triethylamine (1.5 ml, 10.59 mmol) at room temperature for 18h. The reaction mixture was filtered, reduced *in vacuo* and purified by chromatography (CH_2Cl_2/ Et_2O 9:1) to give **7** as a white solid (3.24g, 84%): $[\alpha]^{24}_D$ +5 (*c* 20 in $CHCl_3$); m.p. 161°C; Rf 0.07 (CH_2Cl_2/Et_2O 9:1); $\nu_{max}(CHCl_3)/cm^{-1}$ 2902-2985 (CH), 1753 (CO); δ_H(500 MHz; $CDCl_3$) 1.96 and 2.03 (6H, 2xs, 2xAc), 2.04 (6H, 2xs, 2xAc), 2.09, 2.11, 2.15 (9H, 3xs, 3xAc), 3.64 (1H, ddd, *J* 2.0, 5.6, 9.9, 5-H), 3.75 (1H, dd, *J* 9.5, 9.5, 4-H), 3.86 (1H, ddd, *J* 1.0, 7.3, 7.3, 5'-H), 4.05-4.14 (3H, m, 6-Ha, 6'-Ha, 6'-Hb), 4.48 (1H, d, *J* 7.9, 1'-H), 4.53 (1H, dd, *J* 2.0, 11.9, 6-Hb), 4.68 (1H, d, *J* 10.1, 1-H), 4.90 (1H, dd, *J* 9.6, 9.6, 2-H), 4.95 (1H, dd, *J* 3.4, 10.4, 3'-H), 5.10 (1H, dd, *J* 7.9, 10.4, 2'-H), 5.22 (1H, dd, *J* 9.1, 9.1, 3-H), 5.34 (1H, dd *J* 0.9, 3.4, 4'-H), 7.28-7.33 (3H, m, Ph), 7.43-7.50 (2H, m, Ph); δ_C(50 MHz, $CDCl_3$) 20.35, 20.47, 20.62 (7 CH_3), 60.79, and 62.10 (2 CH_2), 66.59, 69.04, 69.93, 70.21, 70.74, 73.82, 76.13 and 76.55 (8 CH), 85.45 (1-C), 101.08 (1'-C), 128.45 (CH, Ph), 129.06 (2 CH, Ph), 131.93 (C, Ph), 133.05 and 133.17 (2 CH, Ph), 169.31, 169.83, 169.98, 170.32, 170.42 and 170.60 (7 CO); *m/z* (DCI) 746 (MNH_4^+, 7%), 331 [$(M-397)^+$, 100].

Phenyl 1-*deoxy*-4-O-(β-D-*galactopyranosyl*)-1-*thio*-β-D-*glucopyranoside* **8**

To a solution of **7** (3.23 g, 4.43 mmol) in CH_2Cl_2/MeOH (1:1.4, 24 ml) was added a 0.2M sodium methoxide solution (8.85 ml, 1.77 mmol). The reaction mixture was stirred at room temperature for 1.7h, neutralized with amberlite IR-120 (H^+) resin, filtered and concentrated *in vacuo* to 5 ml leading to the precipitation of **8** as a white solid which was collected by filtration (1.58 g, 82%). The filtrate was reduced *in vacuo* and chromatographed (MeOH/$CHCl_3$/H_2O 4:5:1) to give compound **8** (222 mg, 12%): $[\alpha]^{24}_D$ -44.3 (*c* 1.5 in

MeOH); m.p. 126°C; Rf 0.33 (MeOH/$CHCl_3$/H_2O 4:5:1); ν_{max} (KBr)/cm^{-1} 3402 (OH), 2940-2880 (CH); δ_H(500 MHz; CD_3OD) 3.28 (1H, dd, *J* 8.6, 9.6, 2-H), 3.43-3.46 (1H, m, 5-H), 3.48 (1H, dd, *J* 3.3, 9.7, 3'-H), 3.52-3.59 (4H, m, 3-H, 4-H, 2'-H, 5'-H), 3.69 (1H, dd, *J* 4.6, 11.5, 6'-Ha), 3.77 (1H, dd, *J* 7.5, 11.5, 6'-Hb), 3.81 (1H, d, *J* 3.2, 4'-H), 3.83 (1H, dd, *J* 4.3, 12.3, 6-Ha), 3.90 (1H, dd, *J* 2.5, 12.3, 6-Hb), 4.36 (1H, d, *J* 7.6, 1'-H), 4.61 (1H, d, *J* 9.8, 1-H), 7.24-7.32 (3H, m, Ph), 7.54-7.57 (2H, m, Ph); δ_C(50 MHz, CD_3OD) 61.39 and 61.92 (2 CH_2), 69.78, 72.02, 72.90, 74.24, 76.58, 77.45, 79.63, 80.01 (8 CH), 88.66 (1-C), 104.39 (1'-C), 128.10 (CH, Ph), 129.55 (2 CH, Ph), 132.63 (2 CH, Ph), 134.28 (C, Ph); *m/z* (FAB^+) Found: 457.1145 (MNa^+), $C_{18}H_{26}O_{10}SNa^+$ requires 457.1144.

Phenyl 1-*deoxy*-1-*thio*-4-O-(3'-O-p-*toluenesulfonyl*-β-D-*galactopyranosyl*)-β-D-*glucopyranoside* **9** and *Phenyl* 1-*deoxy*-1-*thio*-4-O-(3'-6'-*di*-O-p-*toluenesulfonyl*-β-D-*galactopyranosyl*)-β-D-*glucopyranoside* **11**

Compound **8** (50 mg, 115 μmol) and Bu_2SnO (43 mg, 169 μmol) were stirred in refluxing MeOH (1 ml), under nitrogen for 1h. The solvent was removed *in vacuo* and the dry dibutylstannylene complex was dissolved in THF (1 ml). Bu_4NBr (18.5 mg, 58 μmol) and *p*-toluenesulfonyl chloride (329 mg, 1.72 mmol) were added and the mixture heated under reflux for 1h. The solvent was removed *in vacuo* and the residue chromatographed (CH_2Cl_2/MeOH 10:1) to give some starting material (4.7 mg, 9%), **9** as a colourless oil containing some butylstannyl derivatives (54.5 mg, ~75%) and **11** which was chromatographed again twice (CH_2Cl_2/Et_2O 10:1, then CH_2Cl_2/Et_2O 17:1) leading to a colourless gum (12.8 mg, 15%): **9**: Rf 0.09 (MeOH/CH_2Cl_2 1:10); ν_{max} ($CDCl_3$)/cm^{-1} 3369 (OH), 2966, 2878 (CH), 1599 (C=C), 1354, 1177 (SO_2); δ_H(500 MHz; $CDCl_3$) 2.38 (3H, s, Me), 3.27 (1H, m, OH), 3.43-3.45 (2H, m, 2-H, 5-H), 3.58-3.59 (1H, m, 5'-H), 3.67-3.72 (2H, m, 3-H, 4-H), 3.80-3.88 (4H, m, 6-Ha, 6-Hb, 6'-Ha, 6'-Hb), 3.97 (1H, dd, *J* 9.1, 13.2, 2'-H), 4.09 (1H, s, 4'-OH), 4.18 (1H, s, OH), 4.29 (1H, s, 2'-OH), 4.43-4.50 (3H, m, 3'-H, 2xOH), 4.51 (1H, d, *J* 7.8, 1'-H), 4.67 (1H, d, *J* 9.7, 1-H), 5.10 (1H, s, OH), 7.22-7.29 (5H, m, Ar), 7.50 (2H, d, *J* 6.9, Ar), 7.82 (2H, d, *J* 8.2, Ar); δ_C(125.78 MHz, $CDCl_3$) 21.64 (CH_3), 61.29 and 61.55 (2 CH_2), 68.03, 68.27, 72.13, 74.24, 76.34, 78.46 and 82.85 (7 CH), 87.41 (1-C), 103.13 (1'-C), 128.00 (2 CH, Ar), 128.89 (3 CH, Ar), 129.90 (2 CH, Ar), 131.96 (2 CH, Ar), 132.94 (C, Ar), 133.22 (C, Ar), 144.94 (C, Ar); *m/z* (FAB^+) 573 [$(M\text{-}CH_3)^+$, 1%], 471 [$(M\text{-}117)^+$, 18], 242 [$(M\text{-}346)^+$, 53], 155 [$(M\text{-}433)^+$, 87], 91 (CH_3Ph^+, 100); **11**: $[\alpha]^{25}_D$ -14.9 (*c* 2.3 in MeOH); Rf 0.40 (MeOH/CH_2Cl_2 1:1); ν_{max} ($CDCl_3$)/cm^{-1} 3500 (OH), 2960, 2880 (CH), 1599 (C=C), 1366, 1178 (SO_2); δ_H(500 MHz; $CDCl_3$) 2.43 (6H, s, 2xMe), 2.80 (1H, t, *J* 6.0, 6-OH), 3.19 (1H, d, *J* 2.2, 2-OH), 3.23 (1H, d, *J* 4.6, 4'-OH), 3.38-3.44 (2H, m, 2-H, 5-H), 3.57-3.65 (2H, m, 3-H, 4-H), 3.83-3.90 (5H, m, 2'-H, 2'-OH, 5'-H, 6-Ha, 6-Hb), 4.04 (1H, dd, *J* 3.7, 3.9, 4'-H), 4.09 (1H, d, *J* 1.3, 3-OH), 4.17 (1H, dd, *J* 7.1, 10.6, 6'-Ha), 4.21 (1H, dd, *J* 5.3, 10.7, 6'-Hb), 4.43-4.47 (2H, m, 1'-H, 3'-H), 4.59 (1H, d, *J* 9.8, 1-H), 7.28-7.51 (7H, m, Ar), 7.51 (1H, d, *J* 1.7, Ar), 7.52 (1H, d, *J* 2.2, Ar), 7.78 (2H, d, *J* 8.3, Ar), 7.83 (2H, d, *J* 8.3, Ar); δ_C(125.78 MHz, $CDCl_3$) 21.64 (2 CH_3), 61.91 (CH_2), 67.11 (CH), 67.69 (CH_2), 68.29 (CH), 71.84 (CH), 71.91 (CH), 76.18 (CH), 78.16 (CH), 79.95 (CH), 82.08 (CH), 87.42 (1-C), 103.11 (1'-C), 128.03 (4 CH, Ar), 128.98 (2 CH, Ar), 130.02 (5 CH, Ar), 132.02 (C, Ar), 132.16 (C, Ar), 132.48 (2CH, Ar), 132.72 (C, Ar), 145.39 (C, Ar), 145.53 (C, Ar); *m/z* (MALDI) Found: 765.1309 (MNa^+), $C_{32}H_{38}S_3O_{14}Na^+$ requires 765.1321.

Phenyl 2,3,6-*tri*-O-*acetyl*-4-O-(2',4',6'-*tri*-O-*acetyl*-3'-O-p-*toluenesulfonyl*-β-D-*galactopyranosyl*)-1-*deoxy*-1-*thio*-β-D-*glucopyranoside* **10**

Crude compound **9** (15.3 mg, <26 μmol) was stirred in pyridine/Ac_2O 2:1 (300μl), at room temperature for 20h. The reaction mixture was reduced *in vacuo* and chromatographed [petroleum ether (b.p. 40-60°C)/ethyl acetate 1:1] leading to **10** as a colourless foam (14.2 mg, 65%): $[\alpha]^{25}_D$ -3.0 (*c* 0.9 in $CHCl_3$); Rf 0.26 [petroleum ether (b.p. 40-60°C)/ethyl acetate 1:1]; ν_{max} ($CHCl_3$)/cm^{-1} 2960, 2860 (CH), 1753 (C=O), 1599 (C=C), 1373, 1179 (SO_2), 1225 (C-O); δ_H(500 MHz; $CDCl_3$) 1.93, 2.01, 2.04, 2.05, 2.08, 2.11 (18H, 6xs, 6xAc), 2.44 (3H, s, Me), 3.63 (1H, ddd, *J* 2.0, 5.7, 9.9, 5-H), 3.73 (1H, dd, *J* 9.6, 9.6, 4-H), 3.83 (1H, t, *J* 6.6, 5'-H), 4.05 (2H, d, *J* 6.7, 6'-Ha, 6'-Hb), 4.09 (1H, dd, *J* 5.8, 11.9, 6-Ha), 4.48 (1H, d, *J* 7.9, 1'-H), 4.51 (1H, dd, *J* 2.0, 11.9, 6-Hb), 4.67 (1H, d, *J* 10.1, 1-H), 4.72 (1H, dd, *J* 3.6, 10.1, 3'-H), 4.89 (1H, dd, *J* 9.7, 9.7, 2-H), 5.06 (1H, dd, *J* 7.9, 10.1, 2'-H), 5.20 (1H, dd, *J* 9.1, 9.1, 3-H), 5.45 (1H, d, *J* 3.5, 4'-H), 7.29-7.34 (5H, m, Ar), 7.46-7.48 (2H, m, Ar), 7.73 (2H, d, *J* 8.3, Ar); δ_C(125.78 MHz, $CDCl_3$) 20.50 (2 CH_3), 20.63 (CH_3), 20.76 (2 CH_3), 20.84 (CH_3), 21.68 (CH_3), 60.84 and 62.08 (2 CH_2), 67.24, 68.99, 70.24, 70.71, 73.79, 76.17, 76.32 and 76.61 (8 CH), 85.46 (1-C), 100.74 (1'-C), 127.98 (2 CH), 128.31 (CH, Ar), 128.88 (2 CH, Ar), 129.80 (2 CH, Ar), 131.74 (C, Ar),132.90 (C, Ar), 133.03 (2 CH, Ar), 145.34 (C, Ar), 169.00, 169.39, 169.55, 169.63, 170.24 and 170.33 (6 CO); *m/z* (FAB$^+$) 863 (MNa^+, 6%), 841 (MH^+, 3), 731 [$(M\text{-}SPh)^+$, 17], 443 [$(M\text{-}397)^+$, 18], 169 [$(M\text{-}671)^+$, 33], 109 (PhS^+, 34), 43 (CH_3CO^+, 100).

Phenyl 2,3,6-*tri*-O-*acetyl*-4-O-(2',4'-*di*-O-*acetyl*-3',6'-*di*-O-p-*toluenesulfonyl*-β-D-*galactopyranosyl*)-1-*deoxy*-1-*thio*-β-D-*glucopyranoside* **12**

Compound **11** (11.3 mg, 15 μmol) was treated as described for the synthesis of **10** to give compound **12** as a gum (14 mg, 97 %): $[\alpha]^{25}_D$ +1.8 (*c* 0.9 in $CHCl_3$); Rf 0.35 [petroleum ether (b.p. 40-60°C)/ethyl acetate 1:1]; ν_{max} ($CHCl_3$)/cm^{-1} 2950, 2880 (CH), 1756 (C=O), 1599 (C=C), 1373, 1179 (SO_2), 1225 (C-O); δ_H(500 MHz; $CDCl_3$) 1.91, 1.94, 1.98, 2.09, 2.10 (15H, 5xs, 5xAc), 2.48 (6H, 2xs, 2xMe), 3.63 (1H, ddd, *J* 1.8, 5.5, 9.8, 5-H), 3.72 (1H, dd, *J* 9.7, 9.7, 4-H), 3.87 (1H, t, *J* 6.3, 5'-H), 3.98 (2H, d, *J* 6.3, 6'-Ha, 6'-Hb), 4.06 (1H, dd, *J* 5.6, 11.9, 6-Ha), 4.46 (1H, d, *J* 7.9, 1'-H), 4.50 (1H, dd, *J* 1.9, 12.0, 6-Hb), 4.67 (2H, d, *J* 10.1, 1-H and dd, *J* 2.1, 10.1, 3'-H), 4.88 (1H, dd, *J* 9.7, 9.7, 2-H), 5.03 (1H, dd, *J* 7.9, 10.0, 2'-H), 5.19 (1H, dd, *J* 9.1, 9.1, 3-H), 5.40 (1H, d, *J* 3.5, 4'-H), 7.29-7.32 (3H, m, Ar), 7.34 (2H, d, *J* 8.2, Ar), 7.38 (2H, d, *J* 8.2, Ar), 7.48 (2H, dd, *J* 2.5, 6.1, Ar), 7.72 (2H, d, *J* 8.3, Ar), 7.77 (2H, d, *J* 8.3, Ar); δ_C(125.78 MHz, $CDCl_3$) 20.34, 20.47, 20.68, 20.78 and 20.84 (5 CH_3), 21.70 (2 CH_3), 62.01 and 65.82 (2 CH_2), 67.26, 68.86, 70.30, 70.97, 73.63, 75.96, 76.18 and 76.54 (8 CH), 85.36 (1-C), 100.39 (1'-C),127.98 (2 CH, Ar), 128.00 (2 CH, Ar), 128.26 (CH, Ar), 128.89 (2 CH, Ar), 129.85 (2 CH, Ar), 130.09 (2 CH, Ar), 131.77 and 132.15 (2C, Ar), 132.88 (2 CH, 1C, Ar), 145.42 and 145.52 (2C, Ar), 168.95, 169.19, 169.50, 169.65 and 170.32 (5 CO); *m/z* (LSIMS) 843 [$(M\text{-}SPh)^+$, 5%], 555 [$(M\text{-}397)^+$, 42], 281 [$(M\text{-}671)^+$, 100].

Phenylchlorosulfate **13**

A solution of phenol (17 g, 181 mmol) in dry toluene (380 ml) was stirred with sodium pieces (4.15 g, 180 mmol) in a 100°C oil bath for 2h. When hydrogen formation had finished, the oil bath temperature was increased to 130°C for a further two hours. The reaction mixture was cooled down to 0°C, transferred to a pressure equalising funnel and added slowly (1h) to a cold (0°C) solution of sulfuryl chloride (15 ml, 181

mmol) in toluene (50 ml). The reaction mixture was stirred at room temperature for 16h, washed with H_2O (3x100 ml), dried over Na_2SO_4 and concentrated *in vacuo* leading to a brown oil which was distilled under reduced pressure through a Vigreux column (70-72°C/100 µm Hg, lit.[13a]: 61-65°C/50µm Hg) to give a fraction of colourless oil containing **13** and ~10% phenol (23.3 g, 67%), and a small fraction of pure **13** (1.17 g, 3%): ν_{max} ($CDCl_3$) 1587 (C=C), 1201 (SO_3); δ_H(200 MHz; $CDCl_3$) 7.34-7.57 (m, Ph); δ_C(50 MHz, $CDCl_3$) 121.69 (2 CH), 123.15 (C), 128.84 (CH), 130.28 and 130.42 (2 CH); *m/z* (EI) 194 (M^+, 14%), 192 (M^+, 38), 93[$(M-SO_2Cl)^+$, 33], 65 [$(M-127)^+$, 100].

Phenyl 1-*deoxy*-4-O-(6'-O-*sulfo*-β-D-*galactopyranosyl*)-1-*thio*-β-D-*glucopyranoside* **14**

Compound **8** (50 mg, 115 µmol) was treated as described for the synthesis of **9** and **11** but using $PhSO_3Cl$ (239 µl, 1.7 mmol) instead of *p*-toluenesulfonyl chloride. Chromatography (MeOH/$CHCl_3$/H_2O 4:5:1) gave unreacted starting material and **14** (6.5 mg, 11%) as a white solid: m.p. 176°C (dec.); Rf 0.27 (MeOH/$CHCl_3$/H_2O 4:5:1); ν_{max} (KBr)/cm^{-1} 3427 (OH), 2923 (CH), 1255 (SO_3); δ_H(500 MHz; CD_3OD) 3.29-3.31 (1H, m, 2-H), 3.46-3.89 (4H, m, 4'-H, 5'-H, 6-Ha, 6-Hb), 4.14 (1H, dd, *J* 10.1, 4.5, 6'-Ha), 4.24 (1H, dd, *J* 10.7, 7.9, 6'-Hb), 4.36 (1H, d, *J* 7.4, 1'-H), 4.65 (1H, d, *J* 9.8, 1-H), 7.25-7.32 (3H, m, Ph), 7.55-7.57 (2H, m, Ph); δ_C(125.78 MHz, CD_3OD) 62.18 and 67.96 (2 CH_2), 69.95, 72.29, 73.33, 74.56, 74.76, 77.84, 80.38 and 81.33 (8 CH), 86.74 (1-C), 105.23 (1'-C), 128.52, 129.92, 133.03 (5 CH, Ph), 134.72 (C, Ar); *m/z* (ES^-) 513 [$(M-H)^-$, 100%].

Phenyl 1-*deoxy*-4-O-(3'-O-*sulfo*-β-D-*galactopyranosyl*)-1-*thio*-β-D-*glucopyranoside, sodium salt* **15** and *Phenyl* 1-*deoxy*-4-O-(3',6'-*di*-O-*sulfo*-β-D-*galactopyranosyl*)-1-*thio*-β-D-*glucopyranoside, disodium salt* **16**

Compound **8** (199 mg, 458 µmol) was stirred in refluxing MeOH (4 ml), with Bu_2SnO (116.5 mg, 458 µmol) for 2h under nitrogen. The solvent was reduced *in vacuo* and the dry dibutylstannylene complex was treated with $Me_3N.SO_3$ (132 mg, 920 µmol) in dioxane (4 ml) at room temperature for 30h. The reaction mixture was diluted with MeOH (3 ml), filtered and reduced *in vacuo*. The residue was dissolved in MeOH (3 ml) and loaded onto a cation exchange resin column (AG50W-X8, Na^+, 1x4 cm). The products were eluted with MeOH, the eluant concentrated *in vacuo* and chromatographed (MeOH/$CHCl_3$/H_2O 5:8:1) to give **15** (187.2 mg, 76%) and **16** (29.1 mg, 10%) as white solids: **15**: $[\alpha]^{24}_D$ -26.2 (*c* 4.8 in MeOH); m.p. 215°C (dec.); Rf 0.23 (MeOH/$CHCl_3$/H_2O 5:8:1); ν_{max} (KBr)/cm^{-1} 3402 (OH), 2920, 2880 (CH), 1584 (C=C), 1250 (SO_3^-); δ_H(500 MHz; CD_3OD) 3.28 (1H, dd, *J* 9.7, 8.4, 2-H), 3.43-3.46 (1H, m, 5-H), 3.55 (1H, dd, *J* 8.7, 8.7, 3-H), 3.59 (1H, dd, *J* 9.6, 9.6, 4-H), 3.63 (1H, m, 5'-H), 3.68-3.73 (2H, m, 2'-H, 6'-Ha), 3.77 (1H, dd, *J* 11.5, 7.5, 6'-Hb), 3.85 (1H, dd, *J* 12.3, 4.1, 6-Ha), 3.91 (1H, dd, *J* 12.3, 2.5, 6-Hb), 4.21-4.25 (2H, m, 3'-H, 4'-H), 4.48 (1H, d, *J* 7.8, 1'-H), 4.62 (1H, d, *J* 9.8, 1-H), 7.24-7.32 (3H, m, Ph), 7.54-7.56 (2H, m, Ph); δ_C(125.78 MHz, CD_3OD) 61.98 and 62.43 (2 CH_2), 68.55, 70.87, 73.41, 76.75 and 77.93 (5 CH), 80.51 (2 CH), 81.75 (CH), 89.12 (1-C), 104.82 (1'-C), 128.44, 129.88, 133.01 (5 CH, Ph), 134.92 (C, Ph); *m/z* (FAB^-) Found: 513.0738 [$(M-Na)^-$], $C_{18}H_{25}O_{13}S_2^-$ requires 513.0737; **16**: $[\alpha]^{24}_D$ -29.9 (*c* 1.5 in MeOH); m.p. 194°C (dec.); Rf 0.13 (MeOH/$CHCl_3$/H_2O 5:8:1); ν_{max} (KBr) 3431 (OH), 2928 (CH), 1251 (SO_3); δ_H(500 MHz; CD_3OD) 3.33-3.35 (1H, m, 2-H), 3.51-3.54 (1H, m, 5-H), 3.61 (1H, dd, *J* 8.9, 8.9, 4-H), 3.65 (1H, dd, *J* 8.7, 8.7, 3-H), 3.75 (1H, dd, *J* 7.9, 9.6, 2'-H), 3.87 (1H, dd, *J* 4.4, 12.3, 6-Ha), 3.95 (1H, dd, *J* 2.5, 12.4, 6-Hb), 3.96-3.99 (1H, m, 5'-H), 4.16 (1H, dd, *J* 3.7, 10.8, 6'-Ha), 4.27 (1H, d, *J* 3.3, 4'-H), 4.29-4.36 (2H, m, 3'-H, 6'-Hb), 4.50 (1H, d, *J* 7.8, 1'-H), 4.72 (1H, d, *J* 9.8, 1-H), 7.28-7.36 (3H,

m, Ph), 7.59-7.61 (2H, m, Ph); δ_C(125.78 MHz; CD_3OD) 62.07 (CH_2), 68.29 (CH_2), 70.54, 73.20, 74.47, 77.81, 80.35, 81.31, 81.59 (7 CH), 88.35 (1-C), 105.02 (1'-C), 128.64, 129.98, 133.12 (5 CH, Ph), 134.46 (C, Ph); *m/z* (FAB^-) Found: 615.0117 [$(M-Na)^-$], $C_{18}H_{24}O_{16}SNa^-$ requires 615.0124.

Phenyl 1-*deoxy*-4-O-(6'-O-*sulfo*-β-D-*galactopyranosyl*)-1-*thio*-β-D-*glucopyranoside* **14**, *Phenyl* 1-*deoxy*-4-O-(β-D-*galactopyranosyl*)-6-O-*sulfo*-1-*thio*-β-D-*glucopyranoside* **17** and *Phenyl* 1-*deoxy*-6-O-*sulfo*-4-O-(6'-O-*sulfo*-β-D-*galactopyranosyl*)-1-*thio*-β-D-*glucopyranoside* **18**

A solution of **8** (50 mg, 115 μmol) in DMF (1 ml) was treated with $Me_3N.SO_3$ (33 mg, 230 μmol) and stirred at room temperature for 4 days. The reaction mixture was concentrated *in vacuo* and chromatographed ($MeOH/CHCl_3/H_2O$ 5:8:1) to give unreacted starting material (6.3 mg, 13%) and **14** (10.2 mg, 17%), **17** (5.3 mg, 9%), **18** (10.6 mg, 15%): **17**: Rf 0.22 ($MeOH/CHCl_3/H_2O$ 4:5:1); δ_H(500 MHz; CD_3OD) 3.26 (1H, dd, *J* 9.7, 8.8, 2-H), 3.50-3.51 (2H, m, 2'-H, 4'-H), 3.53 (1H, dd, *J* 8.8, 8.8, 3-H), 3.60 (1H, dd, *J* 9.1, 9.1, 4-H), 3.60-3.62 (1H, m, 5'-H), 3.66-3.69 (1H, m, 5-H), 3.69 (1H, dd, *J* 11.6, 4.8, 6'-Ha), 3.76 (1H, dd, *J* 11.5, 7.4, 6'-Hb), 3.81 (1H, d, *J* 1.4, 3'-H), 4.30 (1H, dd, *J* 11.0, 4.3, 6-Ha), 4.35 (1H, dd, *J* 11.0, 1.9, 6-Hb), 4.48 (1H, d, *J* 7.7, 1'-H), 4.58 (1H, d, *J* 9.8, 1-H), 7.23-7.32 (3H, m, Ph), 7.55-7.59 (2H, m, Ph); δ_C(125.78 MHz, CD_3OD) 62.49 and 67.51 (2 CH_2), 70.43, 72.75, 73.32, 74.82, 77.02, 77.88, 78.26 and 79.62 (8 CH), 88.99 (1-C), 104.65 (1'-C), 128.52, 129.89, 133.42 (5 CH, Ph), 134.59 (C, Ph); *m/z* (ES^-) 513 [$(M-H)^-$]; **18**: m.p. 180°C (dec.); Rf 0.16 ($MeOH/CHCl_3/H_2O$ 4:5:1); ν_{max} (KBr)/cm^{-1} 3435 (OH), 2922 (CH), 1251 (SO_3); δ_H(500 MHz; CD_3OD) 3.28-3.31 (1H, m, 2-H), 3.52-3.57 (4H, m, 2'-H, 4'-H, 3-H, 4-H), 3.70-3.73 (1H, m, 5-H), 3.86 (1H, d, *J* 1.3, 3'-H), 3.88-3.90 (1H, m, 5'-H), 4.14 (1H, dd, *J* 10.7, 4.5, 6'-Ha), 4.24 (1H, dd, *J* 10.7, 8.0, 6'-Hb), 4.28 (1H, dd, *J* 11.0. 4.8, 6-Ha), 4.36 (1H, dd, *J* 11.0, 1.8, 6-Hb), 4.45 (1H, d, *J* 7.7, 1'-H), 4.62 (1H, d, *J* 9.8, 1-H), 7.24-7.32 (3H, m, Ph), 7.57-7.59 (2H, m, Ph); δ_C(125.78 MHz, CD_3OD) 67.70 and 67.95 (2 CH_2), 69.99, 72.51, 73.17, 74.53, 74.75, 77.82, 78.16 and 81.16 (8 CH), 88.59 (1-C), 105.14 (1'-C), 128.55, 129.94, 133.30 (5 CH, Ph), 134.50 (C, Ph); *m/z* (ES^-) 615 [$(MNa-2H)^-$, 54%], 296 [$(M-2H)^{2-}$, 100].

Phenyl 2-*acetamido*-3,4,6-*tri*-O-*acetyl*-1,2-*di*-*deoxy*-1-*thio*-β-D-*glucopyranoside* **19**

To a solution of chloro 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranoside (844 mg, 2.31 mmol) in CH_3CN (10 ml) was added thiophenol (280 μl, 2.72 mmol) and Et_3N (633 μl, 4.54 mmol). The reaction mixture was stirred for 1.5h at room temperature, filtered, concentrated *in vacuo* and chromatographed (AcOEt) leading to **19** as a white solid (968 mg, 95%): $[\alpha]^{24}_D$ -20.4 (*c* 3.3 in $CHCl_3$); m.p. 199°C; Rf 0.35 (AcOEt); ν_{max} ($CDCl_3$)/cm^{-1} 3287 (NH), 2960, 2880 (CH), 1747 (CH_3C=O), 1687(NHC=O), 1514 (NH), 1239 (C-O); δ_H(200 MHz; $CDCl_3$) 1.98, 2.00, 2.02 and 2.07 (12H, 4xs, 4xAc), 3.73 (1H, ddd, *J* 3.0, 5.0, 10.0, 5-H), 4.04 (1H, ddd, *J* 10.0, 10.0, 10.0, 2-H), 4.17-4.21 (2H, m, 6-Ha, 6-Hb),4.87 (1H, d, *J* 10.4, 1-H), 5.05 (1H, dd, *J* 9.7, 9.7, 4-H), 5.24 (1H, dd, *J* 9.7, 9.7, 3-H), 5.81 (1H, d, *J* 9.3, NH), 7.27-7.31 (3H, m, Ph), 7.47-7.52 (2H, m, Ph); δ_C(50 MHz; $CDCl_3$) 20.39 (CH_3), 20.55 (2 CH_3), 23.12 (CH_3), 53.15 (C-H), 62.36 (CH_2), 68.50, 73.66 and 75.61 (3 CH), 86.53 (1-C), 128.10 , 129.03 , 132.45 (5 CH, Ph), 132.76 (C, Ph), 169.61, 170.45, 170.88 and 171.21 (4 CO); *m/z* (CI) Found: 440.1379 (MH^+), $C_{20}H_{26}O_8NS^+$ requires 440.1379.

Phenyl 2-*acetamido*-1,2-*di-deoxy*-1-*thio*-β-D-*glucopyranoside* **20**

A solution of **19** (102.5 mg, 233 μmol) in MeOH (2 ml) was stirred with a 0.6M sodium methoxide solution (149 μl, 89 μmol) at room temperature for 0.5h. The reaction mixture was diluted with MeOH (5 ml) and neutralized with amberlite-IR (H^+) resin. The resin was removed by filtration and washed with MeOH. The filtrate and washings were reduced *in vacuo* leading to **20** as a white solid (72 mg, 99%): $[\alpha]^{23}_D$ +6.6 (*c* 0.8 in MeOH); m.p. 222°C; Rf 0.50 (MeOH/$CHCl_3$/H_2O 4:5:1); ν_{max} (KBr)/cm^{-1} 3360, 3287 (OH, NH), 2940, 2880 (CH), 1651 (C=O), 1541 (NH); δ_H(500 MHz; CD_3OD) 2.02 (3H, s, Ac), 3.33-3.40 (2H, m, 4-H, 5-H), 3.49 (1H, dd, *J* 8.3, 9.8, 3-H), 3.71 (1H, dd, *J* 5.6, 12.1, 6-Ha), 3.79 (1H, dd, *J* 10.1, 10.1, 2-H), 3.90 (1H, dd, *J* 2.2, 12.2, 6-Hb), 4.81 (1H, d, *J* 10.4, 1-H), 7.26-7.33 (3H, m, Ph), 7.51-7.53 (2H, m, Ph); δ_C(125.78 MHz; CD_3OD) 22.96 (CH_3), 56.28 (CH), 62.86 (CH_2), 71.83, 77.43 and 82.12 (3 CH), 88.38 (1-C), 128.17, 129.90, 132.11 (5 CH, Ph), 135.93 (C, Ph), 173.54 (CO); *m/z* (CI) Found: 314.1062 (MH^+), $C_{14}H_{20}O_5NS^+$ requires 314.1062.

Phenyl 2-*acetamido*-1,2-*di-deoxy*-4-O-(β-D-*galactopyranosyl*)-1-*thio*-β-D-*glucopyranoside* **21**

Compound **20** (12.5 mg, 40 μmol) was sonicated with 50 mM sodium cacodylate buffer (pH 7.4, 1 ml) containing $MnCl_2$ (2 mM), and NaN_3 (6 mM) for 15 min. To the white suspension were added BSA (0.9 mg), CIAP (7 U), UDP-glucose (29.9 mg, 48 μmol), UDP-galactose 4-epimerase (4 U) and β-galactosyltransferase (1.07 U). The reaction mixture was incubated at 37°C, after 17h the clear solution was reduced *in vacuo* and the residue chromatographed twice (MeOH/$CHCl_3$/H_2O 4:5:1, then MeOH/$CHCl_3$ 1:4) affording **21** as a white solid (11.3 mg, 60%): $[\alpha]^{23}_D$ +8.3 (*c* 0.9 in H_2O); m.p. 228°C; Rf 0.35 (MeOH/$CHCl_3$/H_2O 4:5:1); ν_{max} (KBr)/cm^{-1} 3409, 3300 (OH, NH), 2940, 2880 (CH), 1646 (C=O), 1548 (NH); δ_H(500 MHz; CD_3OD) 2.01 (3H, s, Ac), 3.46-3.47 (1H, m, 5-H), 3.50 (1H, dd, *J* 3.2, 9.7, 3'-H), 3.55 (1H, dd, *J* 7.5, 9.7, 2'-H), 3.60 (1H, dd, *J* 4.6, 7.5, 5'-H), 3.66-3.68 (2H, m, 3-H, 4-H), 3.70 (1H, dd, *J* 4.5, 11.5, 6'-Ha), 3.78 (1H, dd, *J* 7.5, 11.5, 6'-Hb), 3.83 (1H, d, *J* 3.2, 4'-H), 3.85-3.89 (2H, m, 2-H, 6-Ha), 3.94 (1H, dd, *J* 2.5, 12.3, 6-Hb), 4.41 (1H, d, *J* 7.5, 1'-H), 4.81 (1H, d, *J* 10.5, 1-H), 7.27-7.33 (3H, m, Ph), 7.50-7.52 (2H, m, Ph); δ_C(125.78 MHz; CD_3OD) 22.92 (CH_3), 55.69 (CH), 62.00 and 62.54 (2 CH_2), 70.34, 72.60, 74.83, 75.59, 77,17, 80.52 and 80.67 (7 CH), 88.49 (1-C), 105.03 (1'-C), 128.31, 129.93, 132.32 (5 CH, Ph), 135.74 (C, Ph), 173.37 (CO); *m/z* (DCI) 476 (MH^+, 5%), 366 [$(M\text{-}SPh)^+$, 36], 204 [$(M\text{-}271)^+$, 100].

Phenyl 2-*acetamido*-3,6-*di*-O-*acetyl*-4-O-(2',6'-*di*-O-*acetyl*-β-D-*galactopyranosyl*)-1,2-*di-deoxy*-1-*thio*-β-D-*glucopyranoside* **22**

A solution of compound **21** in pyridine/Ac_2O 2:1 (300μl) was stirred at room temperature for 45h, reduced *in vacuo* and chromatographed (MeOH/$CHCl_3$ 1:9) leading to **22** (1.2 mg, 28%): Rf 0.22 (MeOH/$CHCl_3$ 1:9); δ_H(500 MHz; $CDCl_3$) 1.98, 2.07, 2.10, 2.11 and 2.13 (15H, 5xs, 5xAc), 3.60-3.66 (2H, m, 3'-H, 5'-H), 3.67 (1H, dd, *J* 2.2, 6.2, 5-H), 3.73 (1H, dd, *J* 9.1, 9.1, 4-H), 3.85 (1H, d, *J* 3.4, 4'-H), 4.10-4.18 (2H, m, 2-H, 6-Ha), 4.23 (1H, dd, *J* 6.3, 11.4, 6'-Ha), 4.37 (1H, dd, *J* 6.4, 11.7, 6'-Hb), 4.38 (1H, d, *J* 7.7, 1'-H), 4.52 (1H, dd, *J* 2.1, 11.7, 6-Hb), 4.70 (1H, d, *J* 10.4, 1-H), 4.86 (1H, dd, *J* 7.9, 9.7, 2'-H), 5.08 (1H, dd, *J* 8.7, 9.9, 3-H), 5.68 (1H, d, *J* 9.5, NH), 7.28-7.31 (3H, m, Ph), 7.47-7.49 (2H, m, Ph); *m/z* (DCI) 664 (MH^+, 58%), 534 [$(M\text{-}SPh)^+$, 95], 168 [$(M\text{-}475)^+$, 100].

Phenyl 2-*acetamido*-1,2-*di*-*deoxy*-4-O-(3'-O-*sulfo*-β-D-*galactopyranosyl*)-1-*thio*-β-D-*glucopyranoside, sodium salt* **23**

Compound **21** (43 mg, 90 μmol) was treated as described for the synthesis of **15** using THF (43 h) instead of dioxane to give **23** as a white solid (43.2 mg, 83%): $[\alpha]^{24}_D$ -13 (*c* 2.9 in MeOH); m.p. 205°C (dec.); Rf 0.10 (MeOH/$CHCl_3$/H_2O 5:10:1); ν_{max} (KBr)/cm^{-1} 3403 (OH, NH), 2940, 2880 (CH), 1557 (Ph), 1651 (C=O), 1557 (NH), 1250 (SO_3^-); δ_H(500 MHz; CD_3OD) 2.00 (3H, s, Ac), 3.44 (1H, ddd, *J* 2.6, 4.0, 9.1, 5-H), 3.62-3.66 (3H, m, 3-H, 4-H, 5'-H), 3.66-3.73 (2H, m, 2'-H, 6'-Ha), 3.76 (1H, dd, *J* 7.5, 11.5, 6'-Hb), 3.84-3.88 (2H, m, 2-H, 6-Ha), 3.92 (1H, dd, *J* 2.5, 12.3, 6-Hb), 4.22 (1H, d, *J* 3.2, 4'-H), 4.25 (1H, dd, *J* 3.2, 9.7, 3'-H), 4.51 (1H, d, *J* 7.8, 1'-H), 4.79 (1H, d, *J* 10.5, 1-H), 7.22-7.30 (3H, m, Ph), 7.47-7.89 (2H, m, Ph); δ_C(50 MHz; CD_3OD) 22.25 (CH_3), 55.01 (CH), 61.91 and 61.38 (2 CH_2), 68.06, 70.35, 75.12 and 76.18 (4 CH), 80.05 (2 CH), 81.13 (CH), 87.86 (1-C), 104.25 (1'-C), 127.94 , 129.62 , 131.87 (5 CH, Ph), 135.32 (C, Ph), 173.33 (CO); *m/z* (FAB^-) Found: 554.0999 [$(M-Na)^-$], $C_{20}H_{28}O_{13}S_2^-$ requires 554.1002.

Methyl 3-O-*sulfo*-β-D-*galactopyranoside, sodium salt* **25**

Methyl *β*-D-galactopyranoside **24** (100 mg, 515 μmol) was treated as described for the synthesis of **15** using THF (15 h) instead of dioxane and the product converted to its sodium salt by using MeOH/$CHCl_3$ 1:1 as solvent. Chromatography (MeOH/$CHCl_3$/H_2O 4:5:1) gave **25** as a white gum (142 mg, 93%): $[\alpha]^{23}_D$ +8.3 (*c* 3.6 in MeOH); Rf 0.16 (MeOH/$CHCl_3$/H_2O 4:5:1); ν_{max} (KBr)/cm^{-1} 3436 (OH), 2947 (CH), 1251 (SO_3); δ_H(500 MHz; CD_3OD) 3.53 (3H, s, OMe), 3.56 (1H, dd, *J* 6.09, 6.09, 5-H), 3.67 (1H, dd, *J* 7.9, 8.8, 2-H), 3.74 (1H, d, *J* 5.5, 6-Hb), 3.75 (1H, d, *J* 6.6, 6-Ha), 4.22-4.25 (3H, m, 1-H, 3-H, 4-H); δ_C(50 MHz, CD_3OD) 55.80 (CH_3), 60.93 (CH_2), 67.16, 69.30, 74.91 and 80.58 (4 CH), 104.37 (1-C); *m/z* (FAB^-) Found: 273.0276 [$(M-Na)^-$], $C_7H_{13}O_9S^-$ requires 273.0280.

Methyl 2,4,6-*tri*-O-*acetyl*-3-O-*sulfo*-β-D-*galactopyranoside, sodium salt* **26**

A solution of **25** (17.4 mg, 59 μmol) in Ac_2O/pyridine 1:2 (450 μl) was stirred for 2h and reduced *in vacuo*. The residue was dissolved in toluene (2 ml) and reduced again to give a white solid (24 mg, 97%): Rf 0.47 (MeOH/$CHCl_3$/H_2O 4:5:1); ν_{max} (KBr)/cm^{-1} 2925 (CH), 1737 (C=O), 1263 (SO_3, C-O); δ_H(500 MHz; $CDCl_3$) 1.95, 2.00 and 2.11 (9H, 3xs, 3xAc), 3.51 (3H, s, OMe), 3.84 (1H, dd, *J* 11.1, 11.1, 5-H), 4.31 (1H, d, *J* 10.0, 6-Ha), 4.71 (1H, d, *J* 8.1, 1-H), 4.83 (1H, dd, *J* 3.2, 10.5, 3-H), 5.01 (1H, d, *J* 11.5, 6-Hb), 5.14 (1H, dd, *J* 8.3, 10.2, 2-H), 6.04 (1H, broad s, 4-H); δ_C(125.78 MHz, $CDCl_3$) 14.17, 20.26, 21.05 and 21.13 (4 CH_3), 56.42 (CH_2), 69.57, 70.01, 70.36 and 75.08 (4 CH), 101.04 (1-C), 168.28, 169.82 and 173.09 (3 CO); *m/z* (ES^-) 399 [$(M-Na)^-$, 100%].

3-O-*Sulfo*-β-D-*galactosylceramide, sodium salt* **3** and 3,6-*di*-O-*Sulfo*-β-D-*galactosylceramide, disodium salt* **28**

Galactosylceramide **27** (41.8 mg, 51 μmol) was sulfated as described for **25** using 1.5 equivalent of Bu_2SnO then stirring with $Me_3N.SO_3$ at room temperature for 4 h. The residue was chromatographed twice (MeOH/$CHCl_3$ 1:4 then MeOH/$CHCl_3$/H_2O 5:10:1) to give **3** as a white solid (45.2 mg, 97%) and a trace of **28**: **3**: $[\alpha]^{23}_D$ +2.6 (*c* 1.0 in MeOH); m.p. 184°C (dec.); Rf 0.35 (MeOH/$CHCl_3$/H_2O 5:10:1); ν_{max} (KBr)/cm^{-1} 3435 (OH, NH), 2920, 2851 (CH), 1635 (C=O), 1556 (NH), 1250 (SO_3); δ_H(500 MHz; CD_3OD/$CDCl_3$ 1:1) 0.85 (6H, t, *J* 6.9, 2xCH_3), 1.20-1.35 (54H, m, 27xCH_2), 1.54-1.56 (2H, m,

NHCOCH2C*H*2), 1.97-2.00 (6H, m, 3xCH=CHC*H*2), 2.13-2.16 (2H, t, *J* 7.7, NHCOC*H*2), 3.55 (1H, dd, *J* 5.9, 5.9, 5-H), 3.61 (1H, dd, *J* 3.0, 10.3, OC*H*aHbCNH), 3.70-3.80 (3H, m, 6-Ha, 6-Hb, 2-H), 3.95-3.98 (1H, m, C*H*NH), 4.07 (1H, dd, *J* 7.7, 7.7, C*H*OHCNH), 4.14 (1H, dd, *J* 4.7, 10.3, OCHa*H*bCNH), 4.24-4.27 (2H, m, 3-H, 4-H), 4.32 (1H, d, *J* 7.7, 1-H), 5.30 (2H, t, *J* 4.7, *cis* CH=CH), 5.41 (1H, dd, *J* 7.6, 15.3, CHOHC*H*a=CHb), 5.66 (1H, dt, *J* 7.2, 15.3, CHOHCHa=C*H*b), 7.67 (1H, d, *J* 9.2, NH); δ_C(125.78 MHz; $CD_3OD/CDCl_3$ 1:1) 14.33 (2 CH_3), 23.20 (2 CH_2), 26.61 (CH_2), 27.68 (2 CH_2), 29.87, 29.94 and 30.29 (23 CH_2), 32.49 (2 CH_2), 32.98, 37.02 (2 CH_2), 53.99 (CH), 61.89 (CH_2), 68.02 (CH), 69.50 (CH_2), 70.23, 72.39, 75.41 and 80.94 (4 CH), 103.98 (1-C), 130.04 (C=), 130.37 (C=C), 134.87 (C=), 175.45 (CO); *m/z* (FAB$^-$) Found: 888.6240 [(M-Na)$^-$], $C_{48}H_{90}NO_{11}S^-$ requires 888.6235; **28**: Rf 0.18 ($MeOH/CHCl_3/H_2O$ 5:10:1); ν_{max} (KBr)/cm^{-1} 3435 (OH, NH), 2921, 2851 (CH), 1630 (C=O), 1560 (NH), 1252 (SO_3); δ_H(500 MHz; $CD_3OD/CDCl_3$ 1:1) 0.85 (6H, t, *J* 6.9, 2xCH_3), 1.23-1.32 (54H, m, 27xCH_2), 1.53-1.56 (2H, m, C*H*2CH2CONH), 1.97-2.00 (6H, m, 3xC*H*2CH=CH), 2.14 (2H, t, *J* 7.7, C*H*2CONH), 3.56 (1H, dd, *J* 2.9, 10.3, C*H*aHbCNH), 3.73 (1H, dd, *J* 7.9, 9.5, 2-H) 3.81 (1H, dd, *J* 6.4, 6.4, 5-H), 3.96-3.98 (1H, m, C*H*NH), 4.06 (1H, dd, *J* 7.8, C*H*OHCNH), 4.13-4.23 (3H, m, CHa*H*bCNH, 6-Ha, 6-Hb), 4.25-4.31 (2H, m, 3-H, 4-H), 4.33 (1H, d, *J* 7.7, 1-H), 5.30 (2H, t, *J* 4.7, *cis* CH=CH), 5.41 (1H, dd, *J* 7.6, 15.3, CHOHC*H*a=CHb), 5.66 (1H, dt, *J* 6.7, 15.3, CHOHCHa=C*H*b), 7.74 (1H, d, *J* 8.0, NH); *m/z* (FAB$^-$) Found: 990.5659 [(M-Na)$^-$] and 968.5781 [(MH-2Na)$^-$], $C_{48}H_{89}NO_{14}S_2Na^-$ requires 990.5622 and $C_{48}H_{90}NO_{14}S_2^-$ requires 968.5803.

Benzyl 4-O-(4',6'-O-*benzylidene*-2'-O-*sulfo*-α-D-*glucopyranosyl*)-β-D-*glucopyranoside* **30**

Compound **29** (54mg, 104μmol) was sulfated as described for compound **15** and chromatographed (CH_2Cl_2/MeOH 8 : 2), giving compound **30** as a white gummy solid (54mg, 87%): $[\alpha]^{23}_D$ +26.0 (*c* 1.0 in MeOH); Rf 0.40 (CH_2Cl_2/MeOH 8:2); δ_H (500MHz; CD_3OD) 3.34-3.35 (1H, m, 2-H), 3.40-3.43 (1H, m, 6-H), 3.59 (1H, t, *J* 9.5, 4'-H), 3.69-3.79 (4H, m, 3-H, 6-Hb, 6'-H), 3.86-3.89 (1H, m, 5'-H), 3.90-3.94 (1H, m, 5-H), 3.97 (1H, t, *J* 9.6, 3'-H), 4.26 (1H, dd, *J* 10.1, 4.8, 4-H), 4.33 (1H, dd, *J* 9.6, 4.0, 2'-H), 4.41 (1H, d, *J* 7.9, 1-H), 4.79 (2H, dd, *J* 12.7, 11.8, PhC*H*2), 5.59 (1H, s, PhC*H*), 5.76 (1H, d, *J* 4.01, 1'-H), 7.25-7.51 (10H, m, *Ph*CH2, *Ph*CH); δ_C (125.78MHz; CD_3OD) 62.63, 64.43, 69.69, 70.00, 71.75, 74.80, 76.30, 77.76, 78.20, 79.55, 82.35 (8 CH, 2 CH_2, $PhCH_2$), 98.96, 102.95, 103.06 (1-C, 1'-C, PhCH), 127.51, 128.68, 129.02, 129.17, 129.27, 129.92, 139.04 (10 CH, 2 C, Ph); *m/z* (ES$^-$) 599 [(M-H)$^-$, 100%].

tert *Butyl* [*allyl* 4-O-(4',6'-O-*benzylidene*-2'-O-*sulfo*-α-D-*glucopyranosyl*)-β-D-*glucopyranosid*]*uronate* **32**

Compound **31** (55 mg, 100 μmol) was sulfated as described for compound **15** by stirring with $Me_3N.SO_3$ for 45 h at room temperature. Chromatography (CH_2Cl_2/MeOH 8:2) gave compound **32** as a colourless gum (34 mg, 54%): $[\alpha]^{25}_D$ +29.2 (*c* 1.17 in MeOH); Rf 0.33 (CH_2Cl_2/MeOH 8 : 2); δ_H(500 MHz; CD_3OD) 1.52 (9H, s, C(CH_3)3), 3.27 (1H, dd, *J* 7.9, 9.3, 2-H), 3.54 (1H, t, *J* 9.3, 4'-H), 3.69-3.74 (3H, m, 5'-H, 6'-H), 3.77 (1H, dd, *J* 8.9, 9.0, 3-H), 3.81 (1H, d, *J* 9.6, 5-H), 3.89 (1H, t, *J* 9.5, 3'-H), 3.95 (1H, dd, *J* 8.9, 9.3, 4-H), 4.13-4.17 (1H, m, OCH_2), 4.24-4.32 (2H, m, 2'-H, OCH_2), 4.40 (1H, d, *J* 7.9, 1-H), 5.15-5.17 (1H, m, CH=C*H*2), 5.30-5.34 (1H, m, CH=C*H*2), 5.56 (1H, s, PhC*H*), 5.89 (1H, d, *J* 4.0, 1'-H), 5.91-5.99 (1H, m, C*H*=CH_2), 7.31-7.46 (5H, m, Ph); δ_C(125.78 MHz; CD_3OD) 28.54 [C(*C*H_3)3], 69.50 and 71.47 (2 CH_2), 63.90, 69.82, 74.35, 76.63, 77.06, 77.70, 79.31 and 82.27 (8 CH), 83.73 (*C*Me3), 98.09, 103.01 and

103.76 (1-C, 1'-C, PhCH), 117.69 ($OCH_2CH=CH_2$), 127.54, 128.99 and 129.91 (5 CH, Ph), 135.47 ($OCH_2CH=CH_2$), 139.06 (C, Ph), 169.16 (C=O); *m / z* (FAB^-) Found: 619.1708 [$(M-H)^-$], $C_{26}H_{35}O_{15}S^-$ requires 619.1697.

Allyl 4-O-(4',6'-O-*benzylidene*-2'-O-*sulfo*-α-D-*glucopyranosyl*)-6-O-*tert-butyldimethylsilyl*-β-D-*glucopyranoside* **34**

Compound **33** (50 mg, 86 μmol) was sulfated as described for **15** by stirring with $Me_3N.SO_3$ for 93h at room temperature. Chromatography (CH_2Cl_2/MeOH 8 : 2) gave compound **34** as a colourless gum (32 mg, 52%): $[\alpha]^{25}_D$ +32.23 (*c* 1.03 in MeOH); Rf 0.44 (CH_2Cl_2/MeOH 8 : 2); δ_H(500 MHz; CD_3OD) 0.11 and 0.12 (6H, 2s, $SiMe_2$), 0.92 (9H, s, tBu), 3.23 (1H, dd, *J* 8.1, 8.6, 2-H), 3.35-3.38 (1H, m, 5-H), 3.58 (1H, t, *J* 9.5, 4'-H), 3.72-3.77 (3H, m, 3-H, 4-H, 6'-Ha), 3.86-3.98 (4H, m, 3'-H, 5'-H, 6-H), 4.11-4.16 (1H, m, OCH_2), 4.23 (1H, dd, *J* 4.8, 10.1, 6'-Hb), 4.29 (1H, dd, *J* 4.0, 9.6, 2'-H), 4.30-4.33 (1H, m, OCH_2), 4.33 (1H, d, *J* 7.9, 1-H), 5.14-5.33 (2H, m, $CH=CH_2$), 5.59 (1H, s, PhCH), 5.83 (1H, d, *J* 4.0, 1'-H), 5.92-5.99 (1H, m, $CH=CH_2$), 7.32-7.50 (5H, m, Ph); δ_C(125.78 MHz; CD_3OD) -4.89 and -4.81 ($SiMe_2$), 19.38 (CMe_3), 26.58 (CMe_3), 63.81, 69.73 and 70.89 (3 CH_2), 64.48, 69.89, 74.73, 76.39, 76.84, 78.38, 79.52 and 82.44 (8 CH), 98.78, 102.83 and 103.02 (1-C, 1'-C, PhCH), 117.52 ($OCH_2CH=CH_2$), 127.57, 128.99 and 129.95 (5 CH, Ph), 135.69 ($OCH_2CH=CH_2$), 139.04 (C, Ph); *m / z* (FAB^-) Found: 663.2149 [$(M-H)^-$], $C_{28}H_{42}O_{14}SiS^-$ requires 663.2143.

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(*Received* 16 *September* 1994)