Pergamon

Bioorganic & Medicinal Chemistry 9 (2001) 367–376

BIOORGANIC & MEDICINAL CHEMISTRY

Synthesis of Sulfoquinovosylacylglycerols, Inhibitors of Eukaryotic DNA Polymerase α and β

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Received 19 July 2000; accepted 14 September 2000

Abstract—Sulfoquinovosyldiacylglycerols (SQDGs) and sulfoquinovosylmonoacylglycerols (SQMGs), bearing diverse fatty acids, were synthesized from D-glucose, and were examined for enzymatic inhibitions of DNA polymerase α and β. These results indicated that the carbon numbers of the fatty acids were highly related to the activities, at least in vitro, of eukaryotic DNA polymerase inhibition.

Introduction

The studies on DNA polymerases were initiated in a search for specific inhibitors, because these enzymes are essential for DNA replication, repair and cell divisions.[1–11] During our recent screenings, SQDG and SQMG indicated strong inhibitory activities against eukaryotic DNA polymerase α and β.[1,2] The SQDG and SQMG possessed extensive biological activities such as anti-tumor effects,[12] P-selectin receptor inhibition,[13] inhibition of HIV-RT,[2,14] AIDS-antiviral,[15] and so on.

Although the syntheses against antiviral SQDG and plant SQDG have been achieved,[16,17] we aimed to synthesize SQDGs and SQMGs bearing diverse fatty acids and to examine the relationship between the activities of DNA polymerases and the structure of the fatty acid. We reported the chiral synthesis of SQDGs and determined the C-2 stereochemistry of the natural SQDG from Japanese fern *Athyrium niponicum* by the comparison of ^{1}H NMR data.[18] We also showed the in vitro inhibition of DNA polymerases.[18] It has been indicated that the chirality at C-2 of glycerol was not important, at least in vitro, in DNA polymerase inhibition, because the values of IC_{50} of both compounds were not distinguishable.

In our synthetic plan, an allyl group was α-selectively introduced to the anomeric site of D-glucose initially according to the literature[19] to form the C-3 back glycerol moiety. After several steps, the allyl group was oxidized to glycol by using OsO_4. A problem incurred in this route was that the synthetic SQDG and SQMG were prepared as diastereometric compounds, but we employed this route because there was not much differences for in vitro DNA polymerase inhibition between the respective chiralities.[18] This route appeared to be more attractive than that previously reported, because glycosylation at the advanced stage can be avoided, thereby eliminating the concern about anomeric selectivity.

Result and Discussion

Chemistry

1-*O*-Allyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) was prepared from D-glucose according to a literature procedure.[19] After protection of the secondary hydroxyl groups **1** as benzyl ethers, the reductive cleavage of the benzylidene group at C-6′ treated with $LiAlH_4$, followed by treatment with $AlCl_3$, afforded 4-*O*-benzyl derivative **3**.[20] The tosylation of **3** with TsCl gave **4**. The tosyloxy group at C-6′ of **4** was then converted into a thioacetyl group with potassium thioacetate in EtOH to yield **5**. Oxidation by OsO_4 of the allyl group in **5** provided the diastereomeric diol **6** in the ratio of 45% (2*R*):55% (2*S*)

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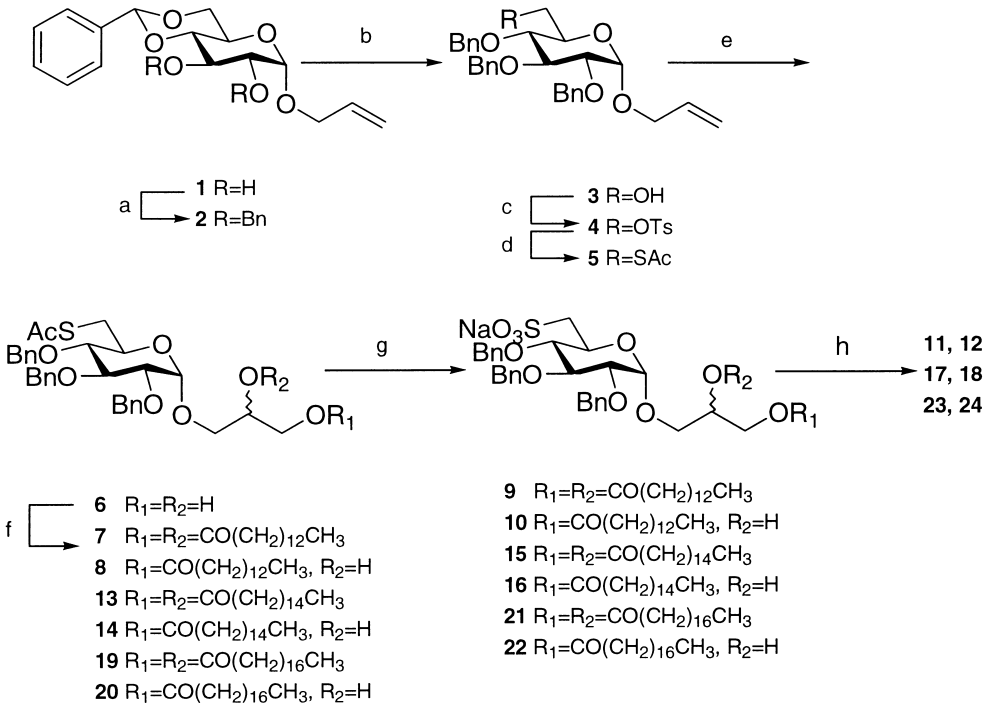
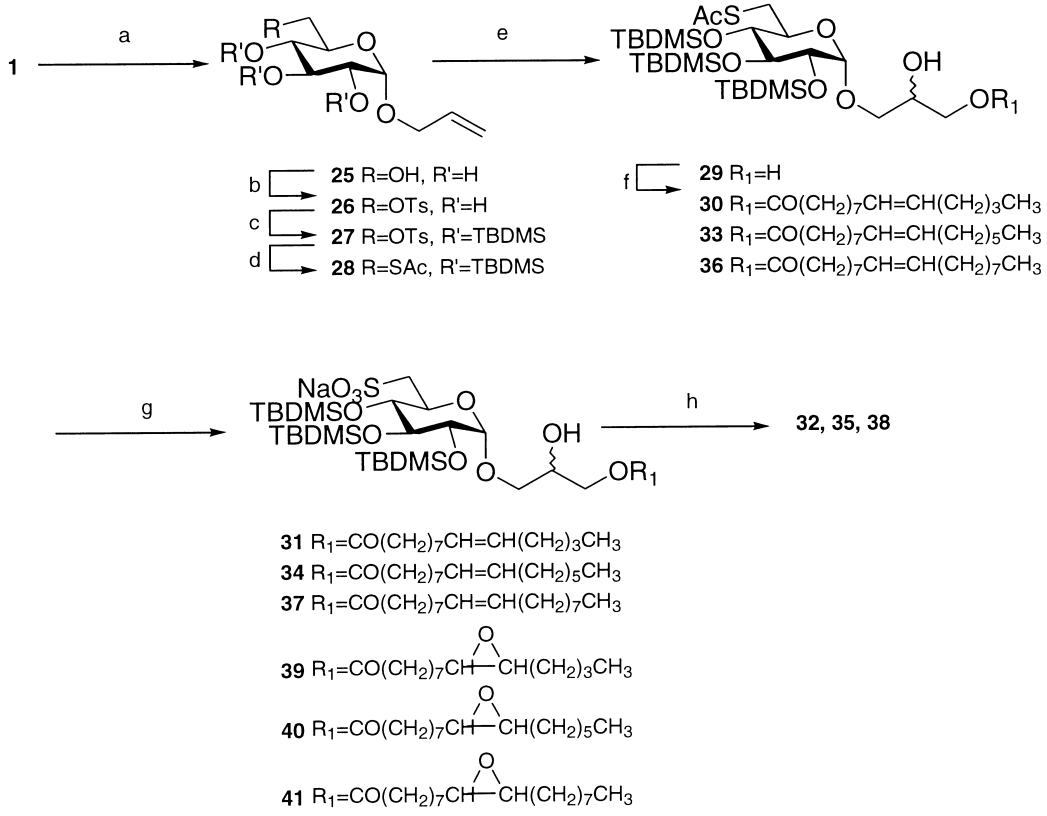
0968-0896/01/$ - see front matter
PII: S0968-0896(00)00252-2

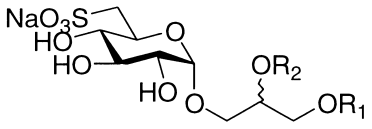


Scheme 1. (a) BnBr, NaH, DMF, 68.2%. (b) $LiAlH_4$, $AlCl_3$, Et_2O, CH_2Cl_2. (c) TsCl, pyridine, DMAP, 72.3% (2 steps). (d) AcSK, EtOH, reflux 88.2%. (e) OsO_4, trimethylamine *N*-oxide, *t*-BuOH, H_2O, 56.9%. (f) Fatty acid, EDCI, DMAP, CH_2Cl_2, 72.9–95.9%. (g) OXONE, AcOH, AcOK, 43.4–92.6% (h) 10% Pd–C, EtOH, H_2, 43.3–86.8%.



Scheme 2. (a) AcOH, H_2O, 80°, 82.4%. (b) *p*-TsCl, pyridine, DMAP, 83.8%. (c) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 91.6%. (d) AcSK, HMPA, 70°, 82.0%. (e) OsO_4, trimethylamine *N*-oxide, *t*-BuOH, H_2O, 88.0%. (f) Fatty acid, EDCI, DMAP, CH_2Cl_2, 61.8–63.8%. (g) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 30% H_2O_2. (h) TFA, AcOH, THF, H_2O, 35–39% (2 steps).

determined by the comparison of ^{1}H NMR data[18] of the synthetic compounds. As Nicolas et al.[21] reported, both AD-mix-α and β preferably gave *S* configuration in the ratio of 10% (2*R*):90% (2*S*). Although this reaction showed the advantage of the enantiomerically selective synthesis of compound **6**, it was not possible for these compounds (2*R* and 2*S*) to be separated on HPLC. We recently reported that the absolute configuration at C-2 of the glycerol moiety was not important, at least in vitro, in DNA polymerase inhibition.[18] Based on this observation, we employed OsO_4 rather than the AD-mix reagent for the oxidation reaction. The acylation of the diastereomeric compound **6** by myristic acid in the presence of EDCI and DMAP gave a mixture of mono- and diester. These two esters were easily separated on silica gel column chromatography into pure monoester **7** and diester **8**. The oxidation of the esters **7** and **8** with OXONE yielded the sodium sulfonate derivatives **9** and **10**, respectively. The catalytic hydrogenation of **9** and **10** with Pd–C gave diester **11** and monoester **12**, respectively. This reaction required a large amount of Pd–C because of the existence of a few impurities which contained sulfur atom. SQDGs (**17** and **23**) and SQMGs (**18** and **24**) were also prepared from **6** in a similar manner (Scheme. 1).



11 $R_1=R_2=CO(CH_2)_{12}CH_3$
12 $R_1=CO(CH_2)_{12}CH_3$, $R_2=H$

17 $R_1=R_2=CO(CH_2)_{14}CH_3$
18 $R_1=CO(CH_2)_{14}CH_3$, $R_2=H$

23 $R_1=R_2=CO(CH_2)_{16}CH_3$
24 $R_1=CO(CH_2)_{16}CH_3$, $R_2=H$

32 $R_1=CO(CH_2)_7CH=CH(CH_2)_3CH_3$, $R_2=H$
35 $R_1=CO(CH_2)_7CH=CH(CH_2)_5CH_3$, $R_2=H$
38 $R_1=CO(CH_2)_7CH=CH(CH_2)_7CH_3$, $R_2=H$

Figure 1. Synthetic products of SQDGs and SQMGs.

Table 1. IC_{50} values of enzymatic inhibitions against eukaryotic DNA polymerase α (pol. α) and β (pol. β)

Compound	IC_{50} (μM)	
	pol. α	pol. β
Fatty acid (linoleic acid)[22]	35	45
Fomitellic acids[25,26]	25–75	50–100
11	1.8	23
12	9.1	350
17	1.2	25
18	4.0	34
23	0.4	37
24	2.1	16
32	34.3	36
35	20.0	22
38	5.2	14

Synthesis of SQMGs bearing unsaturated fatty acids is shown in Scheme 2. Acidic treatment of compound **1** followed by tosylation of the C-6′ hydroxyl group with TsCl afforded **26**. The secondary hydroxyl groups at C-2′, 3′ and 4′ of **26** were protected with TBDMS groups by using trifluoromethanesulfonic acid *t*-butyldimethylsilyl ester (TBDMSOTf) and 2,6-lutidine to give **27**. The tosyloxy group of **27** was then converted into a thioacetyl group with potassium thioacetate in HMPA to yield **28**. This S_N2 reaction did not occur in EtOH as solvent in contrast to the case of compound **4**, in which benzyl groups were used as protective groups at C-2′, 3′ and 4′. The oxidation of **28** with OsO_4 followed by the condensation reaction with myristoreic acid, palmitoleic acid and oleic acid gave **30**, **33** and **36**, respectively. The oxidation of the thioacetyl group of **30**, **33** and **36** with OXONE gave **31**, **34** and **37** in low yield (about 15%), respectively, along with the corresponding epoxides **39**, **40** and **41** as the major products separated on HPLC. Contrary to the OXONE reaction, the oxidation of **30**, **33** and **36** with $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ with 30% H_2O_2 in methanol provided **31**, **34** and **37** in moderate yield (55–60%), respectively. Although this reaction provided a few structurally unknown by-products, it should be noted that the epoxides were not found by measuring the mass spectrum. Compounds **31**, **34** and **37** were deprotected under acidic conditions to afford SQMGs **32**, **35** and **38** in moderate yield, respectively.

Inhibition studies

Synthetic SQDGs (**11**, **17** and **23**) and SQMGs (**12**, **18**, **24**, **32**, **35** and **38**) were tested in an enzymatic inhibition assay of eukaryotic DNA polymerase α and β in vitro. The method was previously described by Mizushina et al.,[22–24] and the results are shown in Table 1. Each compound inhibited eukaryotic DNA polymerase α and β effectively. For DNA polymerase α, SQDGs **11**, **17** and **23** indicated 3–5-fold lower IC_{50} values than those of corresponding SQMGs (**12**, **18**,and **24**), and SQDGs or SQMGs with longer carbon chains were more effective than those with shorter carbon chains; especially, SQMG **24**(C18) provided 4.5-fold effective inhibition compared to that of SQMG **12**(C14). Each SQMG with a double bond in the fatty acid moiety (**32**, **35** and **38**) indicated lower inhibition than those of corresponding SQMGs (**12**, **18** and **24**). We supposed that flexibility of the carbon chain was important for the inhibition of DNA polymerase α (Fig. 1).

For DNA polymerase β, SQMG **38** was the most effective of all synthetic compounds, and this result indicated that both a Z double bond and carbon number in the fatty acid moiety were important for enzymatic inhibition. Finally, SQDG **23** revealed the most selective inhibition of DNA polymerase α compared to DNA polymerase β.

Conclusion

We synthesized SQDGs (**11**, **17** and **23**) and SQMGs (**12**, **18**, **24**, **32**, **35** and **38**), which were effective inhibitors

of eukaryotic DNA polymerase α and β, from D-glucose with a simple method, and investigated inhibitory activities for each enzyme. Compound **23** was the most effective for DNA polymerase α, and compound **38** was the most effective for DNA polymerase β. These results indicated that carbon number in fatty acid moiety of SQDGs or SQMGs was important for enzymatic inhibition, at least in vitro, of eukaryotic DNA polymerases.

Experimental

General methods

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer. Coupling constants are expressed in Hertz (Hz). Low- and high-resolution mass spectra were obtained on a JEOL JMS-700 Mass Spectrometer using fast atom bombardment (FAB) method in *m*-nitrobenzyl alcohol (NBA) or glycerol matrix. Optical rotations were measured on a JASCO P-1010 polarimeter. Column chromatography was performed on silica gel (Wakogel C-200, Tokyo, Japan). Analytical thin-layer chromatography was performed using precoated glass-backed plates (Merck Kieselgel F_{254}, Darmstadt, Germany) and visualized by UV and anisaldehyde in EtOH with H_2SO_4.

1-*O*-Allyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (3). To a solution of 1-*O*-allyl-2,3-di-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside **2** (5.7 g, 12 mmol) in dry dichloromethane (35 mL) and dry diethyl ether (35 mL) was added lithium aluminum hydride (535 mg, 14.1 mmol) with stirring, and the mixture was heated to reflux. A solution of aluminum chloride (2.9 g, 22 mmol) in dry diethyl ether (35 mL) was added dropwise and the mixture was refluxed and stirred for 2 h. After cooling, ethyl acetate (5 mL) was slowly added, followed by water until precipitation was complete. The mixture was diluted with diethyl ether (200 mL) and decanted, the precipitate was washed with diethyl ether (4×50 mL), and the combined organic layers were washed with brine (2×100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The mixture of 4-*O*-benzyl (major) and 6-*O*-benzyl (trace) derivatives was not separated in this step.

1-*O*-Allyl-2,3,4-tri-*O*-benzyl-6-*O*-(4-tolylsulfonyl)-α-D-glucopyranoside (4). To a solution of the crude product **3** in dry pyridine (90 mL) was added 4-toluenesulfonyl chloride (TsCl) (3.1 g 16 mmol) and 4-dimethylaminopyridine (DMAP) (98 mg, 0.80 mmol) under nitrogen atmosphere with stirring. After 20 h at room temperature, the reaction mixture was added to cold water (50 mL), and was diluted with ethyl acetate (100 mL). The aqueous phase was extracted with ethyl acetate (3×50 mL), and the combined organic layers were washed with 1 M HCl (3×100 mL) and brine (2×100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 6:1–3:1 hexanes:ethyl acetate) yielded the tosylate **4** (5.4 g, 8.4 mmol, 72%, over 2 steps): mp 77–79 °C; $[\alpha]_D^{20}$ +28.2 (*c* 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 8.3 Hz, ArH), 7.30 (m, 15H, ArH), 7.13 (m, 2H, ArH), 5.87 (m, 1H, CCH=C), 5.28 (dd, 1H, *J* = 17.2 and 1.4 Hz, C=CH_{2a}), 5.20 (d, 1H, *J* = 10.3 Hz, C=CH_{2b}), 4.99 (d, 1H, *J* = 10.8 Hz, ArCH_{2a}O), 4.91–4.71 (overlapped, m, 4H, ArCH_2O and anomeric H), 4.62 (d, 1H, *J* = 12.1 Hz, ArCH_{2b}O), 4.42 (d, 1H, *J* = 10.7 Hz, ArCH_{2a}O), 4.23 (dd, 1H, *J* = 10.5 and 4.1 Hz), 4.16 (dd, 1H, *J* = 10.5 and 2.0 Hz), 4.08 (dd, 1H, *J* = 12.8 and 5.3 Hz), 3.98 (t, 1H, *J* = 9.3 Hz), 3.93 (dd, 1H, *J* = 12.8 and 6.6 Hz), 3.82 (m, 1H), 3.46 (m, 2H), 2.39 (s, 3H, ArCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 138.5, 137.9, 137.7, 133.4, 132.7, 129.8, 128.4–127.6 (overlapped), 118.4, 95.4, 81.7, 79.6, 76.8, 75.6, 75.0, 73.2, 68.6, 68.5, 68.3, 21.6.

1-*O*-Allyl-2,3,4-tri-*O*-benzyl-6-deoxy-6-thioacetyl-α-D-glucopyranoside (5). To a solution of **4** (11.4 g, 19 mmol) in dry ethanol (250 mL) was added potassium thioacetate (5.6 g, 49 mmol) with stirring, and the mixture was heated to reflux. After 3 h, the reaction mixture was cooled to room temperature and diluted with water (100 mL). The aqueous phase was extracted with ethyl acetate (3×80 mL), and the combined organic layers were washed with brine (2×70 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 10:1 hexanes:ethyl acetate) yielded thioacetate **5** (9.0 g, 8.4 mmol, 88%): mp 61–62.5 °C; $[\alpha]_D^{20}$ +51.8 (*c* 0.98, $CHCl_3$); IR (nuj) 1940, 1880, 1800, 1680, 1600, 1580, 1490, 1160–1120, 1090–1060, 905, 830 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–2.54 (overlapped, m, 15H, ArH), 5.91 (m, 1H, CCH=C), 5.32 (dd, 1H, *J* = 17.1 and 1.4 Hz, C=CH_{2a}), 5.23 (dd, 1H, *J* = 9.5 and 1.0 Hz, C=CH_{2b}), 5.00 (d, 1H, *J* = 10.7 Hz, ArCH_{2a}), 4.90 (d, 1H, *J* = 10.6 Hz, ArCH_{2b}), 4.81 (d, 1H, *J* = 10.7 Hz, ArCH_{2a}), 4.76 (d, 1H, *J* = 12.4 Hz, ArCH_{2b}), 4.74 (d, 1H, *J* = 4.1 Hz, anomeric H), 4.64 (d, 1H, *J* = 12.1 Hz, ArCH_{2a}), 4.61 (d, 1H, *J* = 10.6 Hz, ArCH_{2b}), 4.15 (dd, 1H, *J* = 12.0 and 5.2 Hz), 4.00 (t, 1H, *J* = 9.4 Hz), 3.98 (dd, 1H, *J* = 12.8 and 6.8 Hz), 3.82 (m, 1H), 3.52 (dd, 1H, *J* = 9.7 and 3.6 Hz), 3.42 (dd, 1H, *J* = 13.7 and 2.9 Hz), 3.32 (t, 1H, *J* = 9.3 Hz), 3.05 (dd, 1H, *J* = 13.6 and 7.6 Hz), 2.33 (s, 3H, $SCOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.9, 438.7, 138.1, 138.0, 133.5, 128.4–127.6 (overlapped), 118.4, 95.2, 81.8, 80.6, 80.0, 76.8, 75.7, 75.2, 73.2, 69.5, 68.1, 30.5; LRFABMS *m*/*z* 549.2 $[M+H]^+$; HRFABMS calcd $C_{32}H_{37}O_6S$ $[M+H]^+$ 549.2311, found 549.2330.

3-*O*-(2,3,4-tri-*O*-Benzyl-6-deoxy-6-thioacetyl-α-D-glucopyranosyl)-glycerol (6). To a solution of **5** (8.3 g, 15 mmol) in *tert*-butyl alcohol (80 mL) and water (20 mL) was added 0.04 M osmium tetroxide in *tert*-butyl alcohol (20 mL) and trimethylamine *N*-oxide dihydrate (2.5 g, 23 mmol) with stirring. After 30 h at room temperature, to the resulting mixture was added activated carbon (15 g) and stirred for additional 2 h. The mixture was filtered to remove the activated carbon and the precipitate was washed with ethyl acetate. The filtrate was diluted with water (150 mL) and extracted with ethyl acetate (5×70 mL). The combined organic layers were washed with 0.5 M HCl (2×50 mL) and brine (2×100 mL), dried over anhydrous Na_2SO_4, and

concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 3:1–1:1 hexanes:ethyl acetate) yielded glycol **6** (5.0 g, 8.6 mmol, 57%): mp 68.5–70 °C; $[\alpha]_D^{20}$ +49.1 (*c* 0.56, $CHCl_3$); IR (nuj) 3300, 1680, 1480, 1160–1120, 1180–1140 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (overlapped, m, 15H, ArH), 4.94 (d, 1H, J = 10.8 Hz, $ArCH_{2a}$), 4.88 (d, 1H, J = 10.7 Hz, $ArCH_{2b}$), 4.82 (d, 1H, J = 10.9 Hz, $ArCH_{2a}$), 4.77 (d, 1H, J = 11.9 Hz, $ArCH_{2b}$), 4.70 (d, 1H, J = 3.6 Hz), 4.66 (d, 1H, J = 3.6 Hz), 4.63 (d, 1H, J = 12.0 Hz, $ArCH_{2a}$), 4.62 (d, 1H, J = 11.6 Hz, $ArCH_{2b}$), 3.94 (t, 1H, J = 9.2 Hz), 3.93 (t, 1H, J = 9.2 Hz), 3.80 (m, 1H), 3.71 (dd, 1H, J = 10.8 and 5.1 Hz), 3.54 (dd, 1H, J = 6.1 and 3.8 Hz), 3.52 (dd, 1H, J = 9.6 and 3.7 Hz), 3.49 (m, 1H), 3.41 (dd, 1H, J = 3.0 Hz), 3.37 (dd, 1H, J = 13.5 and 5.9 Hz), 3.31 (t, 1H, J = 9.2 Hz), 3.02 (dd, 1H, J = 13.7 and 7.4 Hz), 2.33 (s, 3H, $SCOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.79, 194.87, 138.4, 137.7, 137.7, 128.6–127.6 (overlapped), 97.53, 97.98, 81.66, 81.71, 80.35, 80.39, 79.84, 79.95, 76.6, 75.7, 75.2, 73.6, 71.1, 70.12, 70.26, 69.78, 69.74, 63.75, 63.68, 30.7, 30.5; LRFABMS *m/z* 583.2 $[M+H]^+$; HRFABMS calcd $C_{32}H_{39}O_8S$ $[M+H]^+$ 583.2366, found 583.2335.

3-*O*-(2,3,4-tri-*O*-Benzyl-6-deoxy-6-thioacetyl-α-D-glucopyranosyl)-1,2-di-*O*-myristoyl-glycerol (7), 3-*O*-(2,3,4-tri-*O*-benzyl-6-deoxy-6-thioacetyl-α-D-glucopyranosyl)-1-*O*-myristoyl-glycerol (8). To a solution of glycol **6** (201 mg, 0.344 mmol) in dry dichloromethane (20 mL) were added 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI) (167 mg, 0.871 mmol), DMAP (68.9 mg, 0.565 mmol), and myristic acid (118 mg, 0.517 mmol) with stirring. After 15 h at room temperature, the reaction mixture was diluted with water (8 mL). The aqueous phase was extracted with dichloromethane (3×10 mL). The combined organic layers were washed with brine (2×10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 7:1–3:1 hexanes:ethyl acetate) yielded **7** and **8** respectively (**7** 149 mg, 0.149 mmol 43.3%, **8** 129 mg, 0.163 mmol, 47.4%): **7** ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 15H, ArH), 5.23 (m, 1H), 5.0–4.5 (overlapped, m, 7H, $ArCH_2O$ and anomeric H), 4.38 (m, 1H), 4.22 (m, 2H), 3.92 (m, 1H), 3.75 (m, 2H), 3.52 (m, 2H), 3.30 (t, 1H), 3.05 (m, 1H), 2.33 (s, 3H, $SCOCH_3$), 2.28 (m, 4H, $OCOCH_2$), 1.59 (m, 4H, $OCOCCH_2$), 1.25 (br, 40H, CH_2), 0.88 (t, 6H, J = 6.3 Hz, CH_3); LRFABMS *m/z* 1041.6 $[M+K]^+$; **8** $[\alpha]_D^{20}$ +99 (*c* 0.07 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 15H, ArH), 4.96–4.60 (m, 7H, $ArCH_2O$ and anomeric H), 4.14 (m, 2H), 4.02 (m, 1H), 3.95 (t, 1H), 3.80 (m, 2H), 3.70 (m, 1H), 3.51 (dd, 1H), 3.39 (m, 1H), 3.02 (dd, 1H), 2.33 (s, 3H, $SCOCH_3$), 2.31 (m, 2H, $OCOCH_2$), 1.59 (m, 2H, $OCOCCH_2$), 1.26 (br, 20H, CH_2), 0.88 (t, 3H, J = 6.2 Hz, CH_3); LRFABMS *m/z* 793.4 $[M+H]^+$; HRFABMS calcd $C_{46}H_{65}O_9S$ $[M+H]^+$ 793.4355, found 793.4349.

3-*O*-(2,3,4-tri-*O*-Benzyl-6-deoxy-6-sulfo-α-D-glucopyranosyl)-1,2-di-*O*-myristoyl-glycerol sodium salt (9). To a solution of **7** (132.7 mg, 0.125 mmol) in glacial acetic acid (7.0 mL) were added potassium acetate (727 mg) and OXONE ($2KHSO_5$, $KHSO_4$, K_2SO_4) (263 mg, 0.428 mmol) with stirring. After 16 h at room temperature, the resulting mixture was diluted with cold water (20 mL). The aqueous phase was extracted with ethyl acetate (5×20 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (2×40 mL) and brine (2×40 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 10:1 dichloromethane:methanol) yielded **9** (116.8 mg, 0.116 mmol, 92.6%): $[\alpha]_D^{20}$ +47.2 (*c* 0.29, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 15H, ArH), 5.28 (m, 1H), 4.95–4.48 (overlapped, m, 7H, $ArCH_2O$ and anomeric H), 4.32 (m, 2H), 4.12 (m, 2H), 3.95 (m, 1H), 3.68 (m, 1H), 3.53 (m, 2H), 3.37 (m, 1H), 3.20 (m, 1H), 3.08 (m, 1H), 2.19 (m, 4H, $OCOCH_2$), 1.50 (m, 4H, $OCOCCH_2$), 1.20 (br, 40H, CH_2), 0.88 (t, 6H, J = 6.4 Hz, CH_3); LRFABMS *m/z* 1007.6 $[M-H]^-$, 779.5 $[M-C_{14}H_{27}O_2]^-$.

3-*O*-(2,3,4-tri-*O*-Benzyl-6-deoxy-6-sulfo-α-D-glucopyranosyl)-1-*O*-myristoyl-glycerol sodium salt (10). To a solution of **8** (118 mg, 0.149 mmol) in glacial acetic acid (2.0 mL) were added potassium acetate (300 mg) and OXONE ($2KHSO_5$, $KHSO_4$, K_2SO_4) (230 mg, 0.375 mmol) with stirring. After 16 h at room temperature, the resulting mixture was diluted with cold water (20 mL). The aqueous phase was extracted with ethyl acetate (5×20 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (2×40 mL) and brine (2×40 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 10:1 dichloromethane:methanol) yielded **10** (90.6 mg, 0.120 mmol, 80.5%): $[\alpha]_D^{20}$ +78.6 (*c* 0.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 15H, ArH), 4.92–4.49 (overlapped, m, 7H, $ArCH_2O$ and anomeric H), 4.27 (m, 2H), 4.10 (m, 2H), 3.91 (m, 1H), 3.82 (m, 1H), 3.63 (m, 1H), 3.49 (m, 1H), 3.37 (m, 1H), 3.19 (t, 1H), 3.09 (m, 1H), 2.20 (m, 2H, $OCOCH_2$), 1.52 (m, 2H, $OCOCCH_2$), 1.28 (br, 20H, CH_2), 0.87 (t, 3H, J = 6.4 Hz, CH_3); LRFABMS *m/z* 797.4 $[M-H]^-$; HRFABMS calcd $C_{44}H_{61}O_{11}S$ $[M-H]^-$ 797.3935, found 797.3942.

3-*O*-(6-Deoxy-6-sulfo-α-D-glucopyranosyl)-1,2-di-*O*-myristoyl-glycerol (11). To a solution of **9** (111 mg, 0.110 mmol) in ethanol (25 mL) was added 10% Pd–C (513 mg), and the resulting mixture was hydrogenated for 16 h with stirring under hydrogen atmosphere. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue was purified by flash chromatography (SiO_2, 65:25:4 chloroform:methanol:water) yielded SQDG **11** (44.4 mg, 0.0601 mmol, 54.6%): ^1H NMR (300 MHz, $CDCl_3$, CD_3OD, D_2O) δ 5.19 (m, 1H), 4.46 (m, 1H), 4.32 (m, 1H), 3.77 (m, 2H), 3.11 (m, 3H), 3.00 (m, 2H), 2.81 (t, 1H, J = 9.1 Hz), 2.64 (dd, 1H, J = 14.3 and 5.1 Hz), 2.02 (m, 4H, $OCOCH_2$), 1.30 (m, 4H, $OCOCCH_2$), 0.99 (br, 40H, CH_2), 0.59 (t, 6H, J = 6.4 Hz, CH_3); LRFABMS *m/z* 737.5 $[M-H]^-$, 527.2 $[M-CH_3(CH_2)_{12}CO]^-$; HRFABMS calcd $C_{37}H_{69}O_{12}S$ $[M-H]^-$ 737.4588, found 737.4522.

3-*O*-(6-Deoxy-6-sulfo-α-D-glucopyranosyl)-1-*O*-myristoyl-glycerol (12). To a solution of **10** (87.2 mg, 0.110 mmol) in ethanol (20 mL) was added 10% Pd–C (323 mg), and the resulting mixture was hydrogenated for 16 h with stirring under hydrogen atmosphere. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue was purified by flash chromatography (SiO_2, 65:25:4 chloroform:methanol:water) yielded SQMG **12** (50.1 mg, 0.0946 mmol, 86.8%): $[\alpha]_D^{20}$ +57.2 (*c* 0.50, chloroform:methanol:water 65:25:4); ^{1}H NMR (300 MHz, $CDCl_3$, CD_3OD, D_2O) δ 4.47 (m, 1H), 3.91 (m, 1H), 3.77 (m, 3H), 3.30 (m, 2H), 3.09 (m, 2H), 3.01 (m), 2.81 (t, 1H, J=9.5 Hz), 2.66 (dd, 1H, J=14.1 and 5.7 Hz), 2.04 (m, 2H, $OCOCH_2$), 1.31 (m, 2H, $OCOCCH_2$), 0.96 (br, 20H, CH_2), 0.60 (t, 3H, J=6.4 Hz, CH_3); LRFABMS *m/z* 527.2 $[M-H]^-$; HRFABMS calcd $C_{23}H_{43}O_{11}S$ $[M-H]^-$ 527.2604, found 527.2632.

3-*O*-(2,3,4-tri-*O*-Benzyl-6-deoxy-6-thioacetyl-α-D-glucopyranosyl)-1,2-di-*O*-palmitoyl-glycerol (13) and 3-*O*-(2,3,4-tri-*O*-benzyl-6-deoxy-6-thioacetyl-α-D-glucopyranosyl)-1-*O*-palmitoyl-glycerol (14). To a solution of glycol **6** (20.3 mg, 0.0343 mmol) in dry dichloromethane (5.0 mL) were added EDCI (19.4 mg, 0.101 mmol), DMAP (5.7 mg, 0.047 mmol), and palmitic acid (14.1 mg, 0.0549 mmol) with stirring. After 16 h at room temperature, the reaction mixture was diluted with water (2 mL). The aqueous phase was extracted with dichloromethane (3×5 mL). The combined organic layers were washed with brine (2×5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 7:1–3:1 hexanes:ethyl acetate) yielded **13** and **14** respectively (**13** 14.7 mg, 0.0139 mmol, 40.5%, **14** 9.1 mg, 0.0111 mmol, 32.3%): **13** mp 51–56 °C; $[\alpha]_D^{20}$ +11.3 (*c* 0.64, $CHCl_3$), IR (nuj) 1735, 1700, 1140, 1060 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.28 (overlapped, m, 15H), 5.2 (m 1H), 4.95 (d, 1H, J=10.8 Hz, $ArCH_{2a}$), 4.88 (d, 1H, J=10.7 Hz, $ArCH_{2b}$), 4.82 (d, 1H, J=9.8 Hz, $ArCH_{2a}$), 4.78 (d, 1H, J=10.8 Hz, $ArCH_{2b}$), 4.70 (d, 1H, J=3.0 Hz, anomeric H), 4.60 (d, 2H, J=11.9 Hz, $ArCH_2$), 4.37 (1H), 4.21 (1H), 3.93 (t, 1H, J=9.3 Hz), 3.79 (1H), 3.76 (1H), 3.73 (1H), 3.50 (1H), 3.40 (1H), 3.30 (t, 1H, J=9.5 Hz), 3.02 (dd, 1H, J=13.8 and 6.4 Hz), 2.33 (s, 3H, $SCOCH_3$), 2.34–2.27 (overlapped, m, 4H, $OCOCH_2$), 1.60 (m, 4H, $OCOCCH_2$), 1.25 (br 48H CH_2), 0.88 (t, 6H, J=6.4 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 179.6, 173.4, 138.6, 138.2, 138.0, 128.6–127.6 (overlapped), 97.17, 96.85, 81.5, 80.3, 80.0, 80.2, 77.2, 75.7, 75.2, 72.98, 73.08, 69.69, 69.79, 66.0, 66.2, 62.4, 62.5, 34.3, 34.2, 34.0, 31.9, 30.8, 30.6, 29.7–29.0 (overlapped), 24.9, 24.7, 22.7, 14.1; LRFABMS *m/z* 1059.7 $[M+H]^+$; **14** $[\alpha]_D^{20}$ +47.0 (*c* 1.13, $CHCl_3$); IR (nuj) 3430, 3050, 3000, 1720, 1680, 1580, 1565, 1480, 1140–1030, 915 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.27 (overlapped, m, 15H, ArH), 4.95 (d, 1H, J=10.8 Hz, $ArCH_{2a}$), 4.89 (d, 1H, J=10.7 Hz, $ArCH_{2b}$), 4.81 (d, 1H, J=11.1 Hz, $ArCH_{2a}$), 4.77 (d, 1H, J=11.8 Hz, $ArCH_{2b}$), 4.70 (d, 1H, J=3.7 Hz, anomeric H), 4.63 (d, 1H, J=10.2 Hz, $ArCH_{2a}$), 4.62 (d, 1H, J=10.7 Hz $ArCH_{2b}$), 4.16 (m, 1H), 4.13 (m, 1H), 3.95 (t, 1H, J=9.2 Hz), 3.8 (m, 1H), 3.75 (1H), 3.68 (1H), 3.51 (dd, 1H, J=9.7 and 3.5 Hz), 3.52 (1H), 3.38 (1H), 3.32 (t, 1H, J=9.2 Hz), 3.04 (dd, 1H, J=13.7 and 7.5 Hz), 2.35 (t, 2H, $OCOCH_2$), 2.32 (s, 3H, $SCOCH_3$), 1.63 (t, 2H, J=6.9 Hz, $OCOCCH_2$), 1.25 (br, 24H, CH_2), 0.88 (t, 3H, J=6.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.8, 173.8, 138.5, 137.8, 137.8, 128.6–127.6 (overlapped), 98.17, 97.75, 81.67, 80.37, 80.00, 97.92, 77.2, 75.69, 75.26, 73.58, 73.46, 70.23, 69.87, 69.9, 68.95, 68.45, 65.07, 64.88, 34.1, 31.9, 30.8, 30.5, 29.7–29.1 (overlapped), 24.9, 22.7, 14.1.

3-*O*-(2,3,4-tri-*O*-Benzyl-6-deoxy-6-sulfo-α-D-glucopyranosyl)-1,2-di-*O*-palmitoyl-glycerol sodium salt (15). To a solution of **13** (133 mg, 0.125 mmol) in glacial acetic acid (7.0 mL) were added potassium acetate (814 mg) and OXONE ($2KHSO_5$, $KHSO_4$, K_2SO_4) (228 mg, 0.371 mmol) with stirring. After 16 h at room temperature, the resulting mixture was diluted with cold water (20 mL). The aqueous phase was extracted with ethyl acetate (5×20 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (2×40 mL) and brine (2×40 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 10:1 dichloromethane:methanol) yielded **15** (57.9 mg, 0.0543 mmol, 43.4%): mp 53–56 °C; $[\alpha]_D^{20}$ +65.6 (*c* 0.34, $CHCl_3$); IR (nuj) 1720, 1490, 1180, 1160–1135, 1070–1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.21 (overlapped, m, 15H, ArH), 5.25 (m, 1H), 4.94 (d, 1H, J=11.7 Hz, $ArCH_{2a}$), 4.90 (d, 1H, J=10.9 Hz, $ArCH_{2b}$), 4.81 (d, 1H, J=11.0 Hz, $ArCH_{2a}$), 4.70 (d, 1H, J=11.2 Hz, $ArCH_{2b}$), 4.50 (2H), 4.58 (d, 1H, J=3.7 Hz), 4.33–3.36 (overlapped, 8H), 3.25 (1H), 3.12 (1H), 2.27–2.18 (overlapped, m, 4H, $OCOCH_2$), 1.53 (br, 4H, $OCOCCH_2$), 1.25 (br, 48H, CH_2), 0.88 (t, 6H, J=6.0 Hz, CH_3); LRFABMS *m/z* 1087.7 $[M+H]^+$.

3-*O*-(2,3,4-tri-*O*-Benzyl-6-deoxy-6-sulfo-α-D-glucopyranosyl)-1-*O*-palmitoyl-glycerol sodium salt (16). To a solution of **14** (52.1 mg, 0.0635 mmol) in glacial acetic acid (2.0 mL) were added potassium acetate (102 mg) and OXONE ($2KHSO_5$, $KHSO_4$, K_2SO_4) (116 mg, 0.190 mmol) with stirring. After 16 h at room temperature, the resulting mixture was diluted with cold water (5.0 mL). The aqueous phase was extracted with ethyl acetate (5×5 mL), and the combined layers were washed with saturated $NaHCO_3$ solution (2×10 mL) and brine (2×10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 10:1 dichloromethane:methanol) yielded **16** (35.1 mg, 0.0424 mmol, 66.8%): $[\alpha]_D^{20}$ +36.4 (*c* 0.30, $CHCl_3$); IR (nuj) 3400, 1720, 1480, 1185, 1155, 1060 cm^{-1}; ^{1}H NMR (300 MHz $CDCl_3$) δ 7.26–7.19 (overlapped, m, 15H, ArH), 4.91–4.54 (overlapped, 6H, $ArCH_2$), 4.71 (1H, anomeric H), 4.28–3.36 (overlapped, 9H), 3.16 (1H), 2.85 (1H), 2.24 (t, 2H, $OCOCH_2$), 1.50 (m, 2H, $OCOCCH_2$), 1.24 (br, 24H, CH_2), 0.87 (t, 3H, CH_3).

3-*O*-(6-Deoxy-6-sulfo-α-D-glucopyranosyl)-1,2-di-*O*-palmitoyl-glycerol (17). To a solution of **15** (360 mg, 0.330 mmol) in ethanol (50 mL) was added 10% Pd–C (1.3 g), and the resulting mixture was hydrogenated for

20 h with stirring under hydrogen atmosphere. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue was purified by flash chromatography (SiO_2, 65:25:4 chloroform:methanol:water) yielded SQDG **17** (129 mg, 0.168 mmol, 50.9%): $[\alpha]_D^{20}$ +54.5 (*c* 0.18, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 5.31 (m, 1H), 4.82 (m, 1H, anomeric H), 4.31 (dd, 1H, *J* = 12.0 and 7.6 Hz), 4.12 (dd, 1H, *J* = 11.9 and 6.7 Hz), 4.04 (m, 2H), 3.63 (m, 2H), 3.46 (dd, 1H, *J* = 9.6 and 3.2 Hz), 3.35 (1H), 3.25 (t, 1H, *J* = 9.3 Hz), 3.06 (dd, 1H, *J* = 14.5 and 7.4 Hz), 2.34 (m, 4H, $OCOCH_2$), 1.62 (m, 4H, $OCOCCH_2$), 1.27 (br, 56H, CH_2), 0.89 (t, 6H, *J* = 6.3 Hz, CH_3); LRFABMS *m/z* 793.8 $[M-H]^-$, 555.4 $[M-CH_3(CH_2)_{14}CO]^-$; HRFABMS calcd $C_{41}H_{77}O_{12}S$ $[M-H]^-$ 793.5214, found 793.5278.

3-*O*-(6-Deoxy-6-sulfo-α-D-glucopyranosyl)-1-*O*-palmitoyl-glycerol (18). To a solution of **16** (202 mg, 0.238 mmol) in ethanol (25 mL) was added 10% Pd–C (1.0 g), and the resulting mixture was hydrogenated for 16 h with stirring under hydrogen atmosphere. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue was purified by flash chromatography (SiO_2, 65:25:4 chloroform:methanol:water) yielding SQMG **18** (57.2 mg, 0.168 mmol, 43.3%): $[\alpha]_D^{20}$ +72.7 (*c* 0.13, MeOH); ^{1}H NMR (300 MHz, CD_3OD) 4.71 (d, 1H, *J* = 3.6 Hz), 4.16 (d, 1H, *J* = 6.8 Hz), 4.16 (d, 1H, *J* = 6.7 Hz), 4.05–3.05 (overlapped, 4H), 3.57 (t, 1H, *J* = 9.6 Hz), 3.02 (t, 1H, *J* = 9.6 Hz), 2.87 (dd, 1H, *J* = 14.4 and 9.3 Hz), 2.29 (t, 2H, *J* = 7.5 Hz, $OCOCH_2$), 1.53 (m, 2H, $OCOCCH_2$), 1.21 (br, 24H, CH_2), 0.82 (t, 3H, *J* = 6.4 Hz, CH_3); LRFABMS *m/z* 555.3 $[M-H]^-$; HRFABMS calcd $C_{25}H_{47}O_{11}S$ $[M-H]^-$ 555.2917, found 555.2854.

3-*O*-(2,3,4-tri-*O*-Benzyl-6-deoxy-6-thioacetyl-α-D-glucopyranosyl)-1,2-di-*O*-stearoyl-glycerol (19) and 3-*O*-(2,3,4-tri-*O*-benzyl-6-deoxy-6-thioacetyl-α-D-glucopyranosyl)-1-*O*-stearoyl-glycerol (20). To a solution of glycol **6** (200 mg, 0.344 mmol) in dry dichloromethane (20 mL) were added EDCI (163 mg, 0.850 mmol), DMAP (65.1 mg, 0.344 mmol), and stearic acid (118 mg, 0.415 mmol) with stirring. After 16 h at room temperature, the reaction mixture was diluted with water (20 mL). The aqueous phase was extracted with dichloromethane (3×20 mL). The combined organic layers were washed with brine (2×20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 7:1–3:1 hexanes:ethyl acetate) yielded **19** and **20** respectively (**19** 164 mg, 0.147 mmol 42.7%, **20** 155 mg, 0.183 mmol, 53.2%): **19** $[\alpha]_D^{20}$ +50.5 (*c* 0.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 15H, ArH), 5.22 (m, 1H), 4.9–4.58 (overlapped, m, 7H, $ArCH_2O$, anomeric H), 4.38 (m, 1H), 4.20 (m, 2H), 3.91 (m, 1H), 3.91 (m, 1H), 3.88 (m, 2H), 3.50 (m, 2H), 3.30 (t, 1H), 3.08 (m, 1H), 2.34 (s, 3H, $SCOCH_3$), 2.31 (m, 4H, $OCOCH_2$), 1.56 (m, 4H, $OCOCCH_2$), 1.25 (br, 56H, CH_2), 0.88 (t, 6H, *J* = 6.4 Hz, CH_3); **20** $[\alpha]_D^{20}$ +39.1 (*c* 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 15H, ArH), 4.96–4.60 (overlapped, m, 7H, $ArCH_2O$, anomeric H), 4.15 (m, 2H), 3.95 (t, 1H, *J* = 9.1 Hz), 3.82 (m, 1H), 3.74 (dd, 1H), 3.70 (m, 1H), 3.51 (dd, 1H), 3.41 (m, 1H), 3.30 (t, 1H), 3.03 (m, 2H), 2.34 (s, 3H, $SCOCH_3$), 2.31 (m, 2H, $OCOCH_2$), 1.64 (m, 2H, $OCOCCH_2$), 1.25 (br, 28H, CH_2), 0.88 (t, 3H, *J* = 6.4 Hz, CH_3); LRFABMS *m/z* 871.6 $[M+Na]^+$.

3-*O*-(2,3,4-tri-*O*-Benzyl-6-deoxy-6-sulfo-α-D-glucopyranosyl)-1,2-di-*O*-stearoyl-glycerol sodium salt (21). To a solution of **19** (120 mg, 0.108 mmol) in glacial acetic acid (10 mL) were added potassium acetate (823 mg) and OXONE ($2KHSO_5$, $KHSO_4$, K_2SO_4) (198 mg, 0.322 mmol) with stirring. After 16 h at room temperature, the resulting mixture was diluted with cold water (20 mL). The aqueous phase was extracted with ethyl acetate (5×20 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (2×40 mL) and brine (2×40 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 10:1 dichloromethane:methanol) yielded **21** (64.7 mg, 0.0577 mmol, 53.4%): $[\alpha]_D^{20}$ +49.8 (*c* 0.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 15H, ArH), 5.30 (m, 1H), 4.85–4.55 (overlapped, m, 7H, $ArCH_2O$, anomeric H), 4.39 (m, 1H), 4.28 (m, 1H), 4.10 (m, 2H), 3.88 (m, 1H), 3.65 (m, 1H), 3.49 (m, 1H), 3.35 (m, 1H), 3.20 (t, 1H), 3.02 (m, 1H), 2.25 (m, 4H, $OCOCH_2$), 1.53 (m, 4H, $OCOCCH_2$), 1.22 (br, 56H, CH_2), 0.88 (t, 6H, *J* = 6.2 Hz, CH_3); LRFABMS *m/z* 1119.7 $[M-H]^-$, 853.5 $[M-C_{18}H_{35}O]^-$.

3-*O*-(2,3,4-tri-*O*-Benzyl-6-deoxy-6-sulfo-α-D-glucopyranosyl)-1-*O*-stearoyl-glycerol sodium salt (22). To a solution of **20** (144.6 mg, 0.170 mmol) in glacial acetic acid (10 mL) were added potassium acetate (823 mg) and OXONE ($2KHSO_5$, $KHSO_4$, K_2SO_4) (314 mg, 0.511 mmol) with stirring. After 16 h at room temperature, the resulting mixture was diluted with cold water (20 mL). The aqueous phase was extracted with ethyl acetate (5×15 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (2×20 mL) and brine (2×20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 10:1 dichloromethane:methanol) yielded **22** (110.1 mg, 0.129 mmol, 75.9%): $[\alpha]_D^{20}$ +43.7 (*c* 0.13, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 15H, ArH), 4.91–4.52 (overlapped, m, 7H, $ArCH_2O$, anomeric H), 4.29 (m, 1H), 4.16 (m, 1H), 4.08 (m, 1H), 3.93 (t, 1H, *J* = 9.0 Hz), 3.80 (m, 2H), 3.62 (m, 1H), 3.49 (m, 1H), 3.36 (m, 1H), 3.18 (m, 2H), 2.22 (m, 2H, $OCOCH_2$), 1.50 (m, 2H, $OCOCCH_2$), 1.25 (br, 24H, CH_2), 0.87 (t, 3H, *J* = 6.4 Hz, CH_3); LRFABMS *m/z* 853.5 $[M-H]^-$, 569.2 $[M-C_{18}H_{37}O_2]^-$.

3-*O*-(6-Deoxy-6-sulfo-α-D-glucopyranosyl)-1,2-di-*O*-stearoyl-glycerol (23). To a solution of **21** (88.5 mg, 0.0789 mmol) in ethanol (20 mL) was added 10% Pd–C (250 mg), and the resulting mixture was hydrogenated for 20 h with stirring under hydrogen atmosphere. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue was purified by flash chromatography (SiO_2, 65:25:4 chloroform:methanol:water) yielding SQDG **23** (47.9 mg,

0.0564 mmol, 71.3%): $[\alpha]_D^{20}$ +38.9 (*c* 0.42, $CHCl_3$:MeOH:H_2O 65:25:4), ^1H NMR (300 MHz, $CDCl_3$, CD_3OD, D_2O) 5.19 (m, 1H), 4.21 (m, 1H), 4.03 (m, 2H), 3.62 (m, 2H), 3.46 (m, 1H), 3.38 (m, 1H), 3.19 (m, 1H), 3.00 (m, 1H), 2.36 (m, 4H, $OCOCH_2$), 1.62 (m, 4H, $OCOCCH_2$), 1.28 (br, 56H, CH_2), 0.89 (m, 6H, CH_3); LRFABMS *m/z* 849.8 $[M-H]^-$, 583.3 $[M-CH_3(CH_2)_{16}CO]^-$.

3-*O*-(6-Deoxy-6-sulfo-α-D-glucopyranosyl)-1-*O*-stearoylglycerol (24). To a solution of **22** (109 mg, 0.128 mmol) in ethanol (20 mL) was added 10% Pd–C (450 mg), and the resulting mixture was hydrogenated for 20 h with stirring under hydrogen atmosphere. The catalyst was removed by filtration and the filtrate was concentrated to dryness. The residue was purified by flash chromatography (SiO_2, 65:25:4 chloroform:methanol:water) yielded SQMG **24** (64.1 mg, 0.110 mmol, 85.9%): $[\alpha]_D^{20}$ +64.8 (*c* 0.58, $CHCl_3$:MeOH:H_2O 65:25:4); ^1H NMR (300 MHz, $CDCl_3$, CD_3OD, D_2O) δ 4.78 (m, 1H, anomeric H), 4.23 (m, 1H), 4.05 (m, 3H), 3.68 (m, 1H), 3.46 (m, 2H), 3.40 (m, 2H), 3.34 (m, 1H), 3.15 (m, 1H), 2.38 (m, 2H, $OCOCH_2$), 1.63 (m, 2H, $OCOCCH_2$), 1.28 (br, 28H, CH_2), 0.89 (t, 3H, *J* = 6.2 Hz, CH_3); LRFABMS *m/z* 583.3 $[M-H]^-$; HRFABMS calcd $C_{27}H_{51}O_{11}S$ $[M-H]^-$ 583.3230, found 583.3223.

1-*O*-Allyl-2,3,4-tri-*O*-(*tert*-butyldimethylsilyl)-6-*O*-(4-tolylsulfonyl)-α-D-glucopyranoside (27). Tosylate **26** (160 mg, 0.428 mmol) was dissolved in dry dichloromethane (2.0 mL). To the solution were added 2,6-lutidine (140 mg, 1.31 mmol) and trifluoromethanesulfonic acid *t*-butyldimethylsilyl ester (400 mg, 1.51 mmol) dropwise at 0 °C under argon atmosphere. After 5 h with stirring, the resulting mixture was diluted with cold water (3 mL) and dichloromethane (5 mL). The aqueous phase was extracted with dichloromethane (2×10 mL). The combined organic layers were washed with brine (2×10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 25:1 hexanes:ethyl acetate) yielded **27** (281.2 mg, 0.392 mmol, 91.6%): $[\alpha]_D^{20}$ +39.0 (*c* 1.05, $CHCl_3$); IR (neat) 1730, 1590, 1240, 1170, 1060, 980, 910, 820, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, 2H, *J* = 8.2 Hz, ArH), 7.29 (d, 2H, *J* = 8.0 Hz, ArH), 5.84 (m, 1H, CCH=C), 5.21 (dd, 1H, *J* = 17.3 and 1.5 Hz, C=CH_2), 5.11 (d, 1H, *J* = 10.4 Hz, C=CH_2), 4.67 (d, 1H, *J* = 2.8 Hz, anomeric H), 4.18–4.05 (overlapped, m, 4H), 3.89–3.77 (overlapped, m, 3H), 3.47 (dd, 1H, *J* = 22.3 and 7.2 Hz), 2.41 (s, 3H, $ArCH_3$), 0.91–0.78 (overlapped, br, 27H, CCH_3), 0.13 to −0.02 (overlapped, br, 18H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 134.7, 129.8, 128.0, 116.5, 95.4, 75.8, 72.9, 71.72, 71.65, 70.1, 68.4, 26.5–25.7 (overlapped), 21.6, 18.3, 18.1, 17.9, −2.9 to −4.9 (overlapped).

1-*O*-Allyl-2,3,4-tri-*O*-(*tert*-butyldimethylsilyl)-6-deoxy-6-thioacetyl-α-D-glucopyranoside (28). To a solution of **27** in dry hexamethylphosphoric triamide (HMPA) (20 mL) was added potassium thioacetate (1.8 g, 16 mmol) with stirring. After 3 h at 70 °C, the resulting mixture was cooled to room temperature and diluted with water (20 mL). The aqueous phase was extracted with ethyl acetate (3×30 mL), and the combined organic layers were washed with brine (2×30 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 50:1 hexanes:ethyl acetate) yielded thioacetate **28** (5.6 g, 9.0 mmol, 82.0%): $[\alpha]_D^{20}$ +60.9 (*c* 1.07, $CHCl_3$); IR (neat) 1670, 1210, 1070, 910, 810, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (m, 1H, CCH=C), 5.28 (dd, 1H, *J* = 17.2 and 1.6 Hz, C=CH_2), 5.13 (dd, 1H, *J* = 10.4 and 1.6 Hz, C=CH_2), 4.73 (d, 1H, *J* = 3.2 Hz, anomeric H), 4.29 (m, 1H), 3.98–3.91 (overlapped, m, 2H), 3.81–3.59 (overlapped, m, 2H), 3.47 (dd, 1H, *J* = 13.1 and 3.0 Hz), 2.84 (dd, 1H, *J* = 13.3 and 9.8 Hz), 2.30 (s, 3H, $SCOCH_3$), 1.20–0.82 (overlapped, m, br, 27H, CCH_3), 0.12 to −0.03 (br, 18H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 134.6, 116.5, 95.5, 76.3, 75.7, 72.7, 71.9, 68.3, 32.5, 30.5, 26.1–25.7 (overlapped), 18.4, 18.1, 17.9, −3.3 to −4.5(overlapped).

3-*O*-[2,3,4-tri-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-6-thioacetyl-α-D-glucopyranosyl]-glycerol (29). To a solution of thioacetate **28** (5.6 g, 9.0 mmol) in *tert*-butyl alcohol (25 mL) and water (10 mL) was added 0.04 M OsO_4 in *tert*-butyl alcohol (15 mL) and trimethylamine *N*-oxide dihydrate (1.5 g, 14 mmol) with stirring. After 48 h at room temperature, to the resulting mixture was added activated carbon (20 g) and stirred for additional 1 h. The mixture was filtered to remove activated carbon and the precipitate was washed with ethyl acetate. The filtrate was diluted with water (50 mL) and extracted with ethyl acetate (5×50 mL). The combined organic layers were washed with 0.5 M HCl (2×50 mL) and brine (2×100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 4:1–2:1 hexanes:ethyl acetate) yielded glycol **29** (5.2 g, 7.9 mmol, 88%): $[\alpha]_D^{20}$ +52.7 (*c* 1.17, $CHCl_3$); IR (neat) 3400, 1680, 1250, 1090, 830, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (1H), 4.02 (1H), 3.85–3.60 (overlapped, 7H), 3.46–3.40 (overlapped, 2H), 2.86 (dd, 1H, *J* = 13.6 and 9.2 Hz), 2.32 (s, 3H, $SCOCH_3$), 0.88–0.79 (overlapped, br, 27H, CCH_3), 0.08 to −0.05 (overlapped, br, 18H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.2, 96.9, 96.5, 76.2, 76.1, 73.6, 73.5, 71.4, 71.2, 70.8, 70.7, 70.7, 70.5, 64.0, 63.9, 32.2, 30.5, 25.9–25.7 (overlapped,), 18.2, 18.0, 17.9,−3.5 to −4.7 (overlapped); LRFABMS *m/z* 677.5 $[M+Na]^+$.

3-*O*-[2,3,4-tri-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-6-thioacetyl-α-D-glucopyranosyl]-1-*O*-myristoreoyl-glycerol (30). To a solution of glycol **29** (851 mg, 1.30 mmol) in dry dichloromethane (40 mL) were added EDCI (1.09 g, 5.71 mmol), DMAP (368 mg, 3.02 mmol), and myristoreic acid (267 mg, 1.18 mmol) with stirring. After 6 h, the reaction mixture was diluted with water (30 mL). The aqueous phase was extracted with dichloromethane (3×30 mL). The combined organic layers were washed with brine (2×50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 25:1–7:1 hexanes:ethyl acetate) yielded **30** (683 mg, 0.792 mmol, 60.9%): $[\alpha]_D^{20}$ +48.1 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.33 (m, 2H), 4.72 (m, 1H, anomeric H), 4.15 (m, 1H),

4.02 (m, 3H), 3.81 (m, 3H), 3.61 (m, 1H), 3.40 (m, 2H), 2.83 (m, 1H), 2.34 (s, 3H, $SCOCH_3$), 2.30 (m, 2H), 1.98 (m, 4H), 1.60 (m, 2H,), 1.29 (br, 12H, CH_2), 0.88 (br, 30H), 0.86–0.31 (overlapped, m, 18H); LRFABMS *m/z* 901 $[M+K]^+$.

3-*O*-[2,3,4-tri-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-6-sulfo-α-D-glucopyranosyl]-1-*O*-myristoreoyl-glycerol sodium salt (31). To a solution of **30** (650 mg, 0.754 mmol) in methanol (140 mL) was added $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (464 mg, 0.375 mmol) in 30% H_2O_2 (10 mL) with stirring. After 48 h at room temperature, the resulting mixture was diluted with water (100 mL). The aqueous phase was extracted with ethyl acetate (5×70 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (2×70 mL) and brine (2×70 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 50:1–10:1 dichloromethane:methanol) yielded crude sulfono derivatives **31**. Some by-products could not be separated at this stage, and this sample was followed by the next reaction.

3-*O*-(6-Deoxy-6-sulfo-α-D-glucopyranosyl)-1-*O*-myristoreoyl-glycerol sodium salt (32). To a solution of **31** (385 mg, 0.432 mmol) in THF (2.0 mL) and water (2.0 mL) were added acetic acid (6.0 mL) and trifluoroacetic acid (0.8 mL) with stirring. After 6 h at room temperature, the resulting mixture was concentrated under reduced pressure. To the precipitate was added methanol (3.0 mL) and concentrated to dryness 3 times. Purification by flash chromatography (SiO_2, 10:1–65:25:4 dichloromethane:methanol, chloroform:methanol:water) yielded SQMG **32** (160 mg, 0.292 mmol, 38.7% over 2 steps); $[\alpha]_D^{20}$ +66.5 (*c* 0.25, $CHCl_3$:MeOH:H_2O 65:25:4); ^1H NMR (300 MHz, $CDCl_3$, CD_3OD, D_2O): δ 5.34 (m, 2H), 4.83 (m, 1H, anomeric H), 4.24 (m, 1H), 4.07 (m, 3H), 3.68 (dd, 1H, *J* = 9.2 and 3.2 Hz), 3.47 (m, 3H), 3.33 (m, 1H), 3.20 (t, 1H, *J* = 9.4 Hz), 3.00 (dd, 1H, *J* = 14.4 and 8.9 Hz), 2.39 (t, 2H, *J* = 7.4 Hz), 2.02 (m, 4H), 1.63 (m, 2H), 1.32 (br, 12H, CH_2), 0.90 (t, 3H, *J* = 6.9 Hz); LRFABMS *m/z* 525.2 $[M-H]^-$; HRFABMS calcd $C_{23}H_{41}O_{11}S$ $[M-H]^-$ 525.2370, found 525.2350.

3-*O*-[2,3,4-tri-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-6-thioacetyl-α-D-glucopyranosyl]-1-*O*-palmitoleoyl-glycerol (33). To a solution of **32** (862 mg, 1.32 mmol) in dry dichloromethane (40 mL) were added EDCI (1.15 g, 6.00 mmol), DMAP (388 mg, 3.18 mmol), and palmitoleic acid (304 mg, 1.20 mmol) with stirring. After 6 h at 0 °C, the reaction mixture was diluted with water (50 mL). The aqueous phase was extracted with dichloromethane (3×50 mL). The combined organic layers were washed with brine (2×70 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 25:1–7:1 hexanes:ethyl acetate) yielded **33** (743 mg, 0.834 mmol, 63.2%); $[\alpha]_D^{20}$ +40.8 (*c* 1.41, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (m, 2H), 4.71 (m, 1H), 4.19–4.00 (overlapped, m, 3H), 3.87–3.67 (overlapped, m, 3H), 3.59 (m, 2H), 3.45 (m, 1H), 2.84 (m, 1H), 2.32 (s, 3H, $SCOCH_3$), 2.25 (m, 2H, $OCOCH_2$), 1.97 (m, 4H,=CCH_2), 1.62 ($OCOCCH_2$), 1.27 (br, 16H, CH_2), 0.86 (m, 30H, CH_3), 0.05 (m, 18H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.14, 195.05, 173.88, 173.80, 129.95, 129.71, 97.01, 96.59, 78.7, 77.2, 76.4, 76.3, 75.9, 73.51, 73.35, 71.25, 70.17, 69.95, 69.08, 98.89, 65.34, 65.22, 34.1, 31.8, 30.5, 29.7–24.8 (overlapped), 22.6, 18.2, 18.0, 17.8, 14.1, −3.5 to −4.8 (overlapped); LRFABMS *m/z* 913.7 $[M+Na]^+$.

3-*O*-[2,3,4-tri-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-6-sulfo-α-D-glucopyranosyl]-1-*O*-palmitoleoyl-glycerol sodium salt (34). To a solution of **33** (715 mg, 0.803 mmol) in methanol was added $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (578 mg, 0.468 mmol) in 30% H_2O_2 (12.0 mL) with stirring. After 67 h at room temperature, the resulting mixture was diluted with water (100 mL). The aqueous phase was extracted with ethyl acetate (5×50 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (2×70 mL) and brine (2×70 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 50:1–10:1 dichloromethane:methanol) yielded crude sulfono derivatives **34**. Some by-products could not be separated at this stage, and this sample was followed by the next reaction.

3-*O*-(6-Deoxy-6-sulfo-α-D-glucopyranosyl)-1-*O*-palmitoleoyl-glycerol sodium salt (35). To a solution of **34** (421 mg, 458 mmol) in THF (2.0 mL) and water (2.0 mL) were added acetic acid (6.0 mL) and trifluoroacetic acid (0.8 mL) with stirring. After 6 h at room temperature, the resulting mixture was concentrated under reduced pressure. To the precipitate was added methanol (3.0 mL) and concentrated to dryness 3 times. Purification by flash chromatography (SiO_2, 10:1–65:25:4 dichloromethane:methanol, chloroform:methanol:water) yielded SQMG **35** (165 mg, 0.286 mmol, 35.6% over 2 steps); $[\alpha]_D^{20}$ +43.0 (*c* 0.90, methanol); ^1H NMR (300 MHz, CD_3OD) δ 5.25 (m, 2H, olefin), 4.68 (1H, anomeric H), 3.97 (m, 2H), 3.50 (m, 1H), 3.32 (m, 2H), 3.20 (m, 2H), 2.98 (t, 1H, *J* = 9.5 Hz), 2.83 (dd, 1H, *J* = 14.4 and 9.2 Hz), 2.51 (m, 2H, $OCOCH_2$), 1.91 (m, 4H, =CCH_2), 1.48 (m, 2H, $OCOCCH_2$), 1.20 (br, 20H, CH_2), 0.78 (t, 3H, *J* = 7.0 Hz, CH_3); LRFABMS *m/z* 553.4 $[M-H]^-$, 299.1 $[M-C_{16}H_{31}O_2]^-$; HRFABMS calcd $C_{25}H_{46}O_{11}S$ $[M-H]^-$ 553.2683, found 553.2692.

3-*O*-[2,3,4-tri-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-6-thioacetyl-α-D-glucopyranosyl]-1-*O*-oleoyl-glycerol (36). To a solution of glycol **29** (929 mg, 1.42 mmol) in dry dichloromethane (40 mL) were added EDCI (1.24 g, 6.47 mmol), DMAP (423 mg, 3.47 mmol), and oleic acid (350 mg, 1.21 mmol) with stirring. After 6 h, the reaction mixture was diluted with water (30 mL). The aqueous phase was extracted with dichloromethane (3×100 mL). The combined organic layers were washed with brine (2×50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 25:1–7:1 hexanes:ethyl acetate) yielded **36** (780 mg, 0.849 mmol, 59.8%); $[\alpha]_D^{20}$ +53.3 (*c* 1.29 $CHCl_3$); IR (neat) 3450, 1730, 1680, 1240, 1080, 820, 770 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.30 (m,

2H, olefin), 4.68 (d, 1H, $J=2.6$ Hz, anomeric H), 3.98–3.92 (overlapped, m, 3H), 3.77–3.64 (overlapped, m, 3H), 3.55 (dd, 1H, $J=10.1$ and 5.5 Hz), 3.47–3.42 (overlapped, m, 3H), 2.81 (dd, 1H, $J=23.0$ and 9.5 Hz), 2.30 (s, 3H, $SCOCH_3$), 2.33 (t, 2H, $J=7.5$ Hz, $OCOCH_2$), 1.96 (m, 4H, $=CCH_2$), 1.59 (m, 2H, $OCOCCH_2$), 1.26–1.21 (br, 20H, CH_2), 0.87–0.79 (overlapped, m, 30H, CH_3), 0.08 to −0.04 (overlapped, m, 18H, $SiCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 173.6, 173.5, 129.9, 129.7, 96.3, 95.9, 76.4, 76.3, 75.8, 75.6, 73.3, 73.1, 73.1, 73.0, 71.4, 71.2, 66.6, 66.0, 62.6, 62.3, 34.3–22.6 (overlapped), 18.2, 18.0, 17.8, 14.1, −4.0 to −4.7 (overlapped); LRFABMS m/z 941.7 $[M+Na]^+$.

3-*O*-[2,3,4-tri-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-6-sulfo-α-D-glucopyranosyl]-1-*O*-oleoyl-glycerol sodium salt (37). To a solution of **36** (732 mg, 0.797 mmol) in methanol (135 mL) was added $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (500 mg, 0.405 mmol) in 30% H_2O_2 (11 mL) with stirring. After 41 h at room temperature, the resulting mixture was diluted with water (100 mL). The aqueous phase was extracted with ethyl acetate (5×50 mL), and the combined organic layers were washed with saturated $NaHCO_3$ solution (2×80 mL) and brine (2×80 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, 50:1–10:1 dichloromethane:methanol) yielded crude sulfono derivatives **37**. Some by-products could not be separated in this step, and this sample was followed by the next reaction.

3-*O*-(6-Deoxy-6-sulfo-α-D-glucopyranosyl)-1-*O*-oleoyl-glycerol sodium salt (38). To a solution of **37** (440 mg, 0.465 mmol) in THF (2.0 mL) and water (2.0 mL) were added acetic acid (6.0 mL) and trifluoroacetic acid (0.8 mL) with stirring. After 6 h at room temperature, the resulting mixture was concentrated under reduced pressure. To the precipitate was added methanol (3.0 mL) and concentrated to dryness 3 times. Purification by flash chromatography (SiO_2, 10:1–65:25:4 dichloromethane:methanol, chloroform:methanol:water) yielded SQMG **38** (175 mg, 0.290 mmol, 36% over 2 steps); $[\alpha]_D^{20}$ +48.3 (*c* 0.52, MeOH); ^1H NMR (300 MHz, $CDCl_3$, CD_3OD, D_2O) δ 5.34 (m, 2H), 4.81 (1H, anomeric H), 4.35 (m, 1H), 4.07 (m, 3H), 3.68 (t, 1H, $J=9.4$ Hz), 3.49 (m, 1H), 3.35 (m, 1H), 3.15 (t, 1H, $J=9.8$ Hz), 2.98 (dd, 1H, $J=14.4$ and 8.8 Hz), 2.38 (m, 2H, $OCOCH_2$), 2.02 (m, 4H, $=CCH_2$), 1.32 (m, 2H, $OCOCCH_2$), 1.18 (br, 20H, CH_2), 0.89 (t, 3H, $J=6.3$ Hz, CH_3); LRFABMS m/z 581.4 $[M-H]^-$, 299.1 $[M-C_{18}H_{35}O_2]^-$; HRFABMS calcd $C_{27}H_{49}O_{11}S$ $[M-H]^-$ 581.2996, found 581.2947.

References and Notes

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