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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Effects of lipophilicity, protecting group and stereochemistry on the antimalarial activity of carbohydrate-derived thiochromans

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Abstract A series of novel carbohydrate-derived thiochromans has been successfully synthesized in order to investigate the influence of alkyl substituents on the aromatic ring of the thiophenol moiety in addition to the effect of protecting groups and stereochemistry on the sugar component of the target molecules. Results from the evaluation of the thiochromans for their antimalarial activity against the chloroquine-sensitive (3D7) strain of *Plasmodium falciparum* suggest that the presence of short chain alkyl substituents, a benzyl ether protecting group and equatorial orientation of the C-4 substituent on the sugar moiety are crucial structural features that impart high antimalarial activity.

Keywords Thiochromans · Antimalarial agents · Effect of lipophilicity · Carbohydrate-derived antimalarial

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Introduction

Malaria is a preventable as well as treatable disease that infects humans through a bite from a female *Anopheles* mosquito infected with *Plasmodium* parasite, yet, the disease still causes avertible deaths especially in poor communities (Greenwood et al. 2008; Barat 2006; O'Meara et al. 2010; Bhatt et al. 2015; Teklehaimanot and Mejia 2008; Amexo et al. 2004). According to the 2016 World Health Organization report, an estimated 212 million cases of malaria occurred worldwide in that year and malaria infection was responsible for an estimated 429,000 deaths globally. Specifically, 92% of those occurred in Africa, followed by 6% in South-East Asia and 2% of the deaths occurring in the Eastern Mediterranean. In addition, 70% of these deaths occurred in children under the age of 5 years (World Health Organization 2016).

There have been substantial developments made to combat the malaria scourge including the provision of insecticide-treated mosquito bed nets, as well as research and development towards an effective antimalarial vaccine and novel drugs (Curtisa et al. 2003; Kulkarni et al. 2007). However, recent reports on the emergence of drug-resistant malarial strains in South-East Asia towards the current antimalarial drug artemisinin poses a global health threat that needs to be addressed through fast tracking the development and biological evaluation of new antimalarial agents, possibly with new modes of action. (Burrows et al. 2013; Hayward 2013; Ashley et al. 2014).

In this regard, our group recently reported the synthesis of novel antimalarial chemotypes depicted in Fig. 1. Structure–activity relationship (SAR) studies showed that sulfone **1** and sulfoxide **2** demonstrated better activity, $< 0.4\,\mu M$ IC_{50}, against chloroquine-sensitive (3D7) and chloroquine resistant (FCR3) *P. falciparum* strains than the

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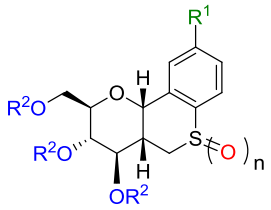


R^1 = ^{t}Bu, R^2 = Bn, n = 2: IC_{50} = 0.39 μM for 3D7 and 0.28 μM for FCR
R^1 = ^{t}Bu, R^2 = Bn, n = 1: IC_{50} = 0.30 μM for 3D7 and 0.33 μM for FCR
R^1 = Me, R^2 = Bn, n = 2: IC_{50} = 2.32 μM for 3D7 and 1.93 μM for FCR
R^1 = ^{t}Bu, R^2 = Bn, n = 0: IC_{50} = > 100 μM for 3D7 and FCR3
R^1 = ^{t}Bu, R^2 = H, n = 2: IC_{50} = > 100 μM for 3D7 and FCR3
R^1 = ^{t}Bu, R^2 = Ac, n = 2: IC_{50} = > 100 μM for 3D7 and FCR3

Fig. 1 The IC_{50} values (μM) of the previously reported carbohydrate-derived thiochromans **1–6** against chloroquine-sensitive (3D7) and -resistant (FCR3) strains of *P. falciparum* (Kinfe et al. 2014)

corresponding carbohydrate-based thiochromans **3–6** (Fig. 1) (Kinfe et al. 2014). These results indicated that the high oxidation state of the sulfur atom (**1** and **2** vs. **4**), the presence of a bulky and lipophilic substituent on the aromatic ring of the thiochroman moiety (**1** vs. **3**), as well as the presence of the benzyl-protecting group of the sugar moiety (**1** and **2** vs. **5** and **6**) were indispensable for the antimalarial activity. On the basis of these SAR studies, we have now designed and synthesized new carbohydrate-derived thiochroman analogs possessing different alkyl substituents, protecting groups and opposite stereochemistry at C-4, in order to further explore their effects. Herein, we report their synthesis and antimalarial activity.

Materials and methods

All the solvents used in the reactions were dried and freshly distilled by appropriate techniques. (Perrin and Armarego 1988) The 2-*C*-iodomethyl-glucosy acetates **13** were synthesized according to previously reported methods and their experimental data were in agreement with the literature. (Gammon et al. 2007) All reagents were purchased from Sigma Aldrich and used as received. All reactions were monitored by thin layer chromatography (TLC) on aluminum-backed Merck silica gel 60 F254 plates using an ascending technique. The plates were visualized by spraying with a 1:1 solution of 5% *p*-anisaldehyde in ethanol and 10% sulfuric acid in ethanol then baking at 150 °C. Gravity column chromatography was done on Merck silica gel 60 (70–230 mesh). Melting points were determined using a Reichert-Jung Thermovarhot-stage microscope and are uncorrected. All proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded as deuteriochloroform solutions using tetramethylsilane as an internal standard on a Bruker Ultrashield (400 MHz) spectrometer. Carbon-13 NMR spectra were recorded on the same instrument at 100 MHz using tetramethylsilane as an internal standard. All chemical shifts are reported in ppm. Anomeric ratios are calculated from the ^{1}H NMR spectroscopy of the crude product. Mass spectra were recorded on a Walters API Quattro Micro spectrometer at the University of Stellenbosch, South Africa.

General procedure for the acylation of benzene

An oven-dried two-necked round bottom flask under nitrogen atmosphere was charged with anhydrous dichloromethane (20 mL) followed by aluminum chloride (4.12 g, 30.9 mmol) and benzene **7** (2.90 mL, 34.0 mmol). A solution of the corresponding acid chloride **8** (30.9 mmol) in dichloromethane (10 mL) was then added in a dropwise fashion over a period of an hour and stirring was continued for 4 h at room temperature. Upon completion of the reaction, the reaction mixture was poured onto a 15 mL ice-cold solution of concentrated HCl (3 M) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were then washed with brine (10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography using a combination of hexane and ethyl acetate in a 19:1 ratio as eluent to afford the corresponding ketone **9**.

Propiophenone (**9a**): colorless oil, 78% (3.23 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01–7.90 (m, 2H, Ar), 7.55 (t, J = 7.3 Hz, 1H, Ar), 7.45 (t, J = 7.4 Hz, 2H, Ar), 3.00 (d, J = 7.2 Hz, 2H, H-2), 1.22 (t, J = 7.2 Hz, 3H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.0 (C=O), 136.1 134.0, 128.1, 128.0 (Ar), 31.8 (C-2), 7.9 (C-3). The spectroscopic data were in agreement with the literature report (Liu et al. 2014).

2-Methyl-1-phenylbutan-1-one (**9b**): colorless oil, 68% (1.63 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90–7.88 (m, 2H, Ar), 7.44–7.40 (m, 1H, Ar), 7.35–7.31 (m, 2H, Ar), 3.32–3.41 (m, 1H, H-3), 1.69–1.79 (m, 2H, H-2), 1.09 (d, J = 6.9 Hz, 3H, H-4), 0.82 (t, J = 7.4 Hz, 3H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 205.1 (C=O), 142.8, 135.9, 127.5 (Ar), 42.0 (C-2), 26.3 (C-3), 16.1 (C-4), 12.0 (C-5). The spectroscopic data were in agreement with the literature report (Alonso et al. 1996).

Phenylhexanone (**9c**): colorless oil, 71% (2.65 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90–7.87 (m, 2H, Ar), 7.44–7.41 (m, 1H, Ar), 7.40–7.37 (m, 2H, Ar), 2.88 (t, J = 7.2 Hz, 2H, H-2), 1.69–1.64 (m, 2H, H-3), 1.31–1.27 (m, 4H, H-4, and H-5), 0.84 (t, J = 7.2 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.0 (C=O), 137.5, 133.3, 129.0, 128.5 (Ar), 39.0 (C-2), 32.0 (C-4), 24.5 (C-3), 22.9 (C-5), 14.4 (C-6). The spectroscopic data were in agreement with the literature report (Ruan et al. 2008).

Phenyloctanone (**9d**): colorless oil, 78% (2.01 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (t, J = 7.1 Hz, 2H, Ar),

7.11 (t, $J = 7.1$ Hz, 3H, Ar), 2.54 (t, $J = 7.7$ Hz, 2H, H-2), 1.63–1.55 (m, 2H, H-3), 1.33–1.22 (m, 8H, H-4, H-5, H-6, and H-7), 0.82 (t, $J = 8.0$ Hz, 3H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.1 (C=O), 142.9, 128.3, 128.1, 125.5 (Ar), 36.0 (C-2), 31.9 (C-3), 29.5 (C-4), 29.2 (C-5), 22.6 (C-6 and C-7), 14.1 (C-8). The spectroscopic data were in agreement with the literature report (Rahaim and Maleczka 2011).

Phenyloctadecanone (**9e**): colorless oil, 73% (1.98 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (t, $J = 7.2$ Hz, 2H, Ar), 7.11 (t, $J = 7.2$ Hz, 3H, Ar), 2.54 (t, $J = 7.8$ Hz, 2H, H-2), 1.33–1.22 (m, 30H, H-3 to H-17), 0.82 (t, $J = 8.0$ Hz, 3H, H-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.8 (C=O), 137.5, 133.3, 129.0, 128.5 (Ar), 39.8 (C-2), 31.8 (C-16), 29.6 (C-5–9), 29.5 (C-10–15), 29.4 (C-4), 29.3 (C-3), 22.7 (C-17), 14.1 (C-18). The spectroscopic data were in agreement with the literature report (Li and Zou 2015).

General procedure for Clemmensen reduction of the ketones 9a–e

To a solution of ketone **9** (14.9 mmol) in water (10 mL) was added Zn dust (2.92 g, 44.7 mmol) and concentrated HCl (3.69 mL, 44.7 mmol). The reaction mixture was then stirred at 100 °C until completion (6 h). The reaction was allowed to cool down and extracted with diethyl ether (3 × 10 mL). The combined organic layers were then washed with a saturated $NaHCO_3$ (3 × 10 mL) and finally with 10 mL of cold brine solution. The organic layer was dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude product was then purified by silica gel column chromatography using hexane as solvent to yield the corresponding alkyl substituted benzene **10**.

Propylbenzene (**10a**): colorless oil, 80% (1.43 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42–7.01 (m, 5H, Ar), 3.05–2.94 (m, 2H, H-1), 2.01–1.80 (m, 2H, H-2), 0.90 (t, $J = 7.4$ Hz, 3H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.8, 128.5, 128.3, 125.7 (Ar), 38.2 (C-1), 24.1 (C-2), 139 (C-3). The spectroscopic data were in agreement with the literature report (Eisch and Dutta 2005).

2-Methylbutylbenzene (**10b**): colorless oil, 75% (1.06 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, $J = 7.6$ Hz, 2H, Ar), 7.60–7.41 (m, 3H, Ar), 3.48–3.35 (m, 2H, H-1), 1.92–1.78 (m, 2H, H-2), 1.64–1.55 (m, 1H, H-3), 1.17 (d, $J = 6.8$ Hz, 3H, H-4), 0.90 (t, $J = 7.4$ Hz, 3H, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.7, 129.2, 128.1, 125.6 (Ar), 43.3 (C-1), 36.7 (C-2), 29.2 (C-3), 18.9 (C-4), 11.5 (C-5). The spectroscopic data were in agreement with the literature report (Gonzalez et al. 2008).

Hexylbenzene (**10c**): colorless oil, 77% (1.73 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (t, $J = 6.8$ Hz, 2H, Ar), 7.20–7.12 (m, 3H, Ar), 2.60 (t, $J = 7.6$ Hz, 2H, H-1), 1.65–1.50 (m, 2H, H-2), 1.40–1.19 (m, 6H, H-3, H-4, and H-5), 0.88 (t, $J = 6.8$ Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.4, 128.9, 127.7, 126.0 (Ar), 35.9 (C-1), 31.6 (C-4), 31.0 (C-2), 29.0 (C-3), 23.6 (C-5), 14.1 (C-6). The spectroscopic data were in agreement with the literature report (Ackermann et al. 2010).

Octylbenzene (**10d**): colorless oil, 56% (1.03 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (t, $J = 7.0$ Hz, 2H, Ar), 7.11 (t, $J = 7.0$ Hz, 3H, Ar), 2.58–2.51 (m, 2H, H-1), 1.65–1.51 (m, 2H, H-2), 1.25–1.20 (m, 10 H, H-3 to H-7), 0.82 (t, $J = 7.6$ Hz, 3H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.0, 129.0, 128.6, 126.1 (Ar), 36.2 (C-1), 32.3 (C-6), 32.0 (C-2), 31.2 (C-4), 29.9 (C-3), 29.6 (C-5), 22.9 (C-7), 14.6 (C-8). The spectroscopic data were in agreement with the literature report (Soulé et al. 2013).

Octadecylbenzene (**10e**): colorless oil, 69% (1.23 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21–7.30 (m, 5H, Ar), 2.71 (t, $J = 7.8$ Hz, 2H, H-1), 1.68–1.64 (m, 2H, H-2), 1.16–1.49 (m, 30H, H-3 to H-17), 0.92 (t, $J = 6.8$ Hz, 3H, H-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144,1, 129.2, 128.3, 126.1 (Ar), 35.8 (C-1), 32.2 (C-2), 31.4 (C-16), 30.1 (C-3–14), 29.2 (C-15), 27.3 (C-17), 14.1 (C-18). The spectroscopic data were in agreement with the literature report (Khamatnurova et al. 2014).

General procedure for the sulfonation of benzene derivatives 10a−e

To a solution of alkyl benzene **10** (11.9 mmol) in dichloromethane (10 mL) was added chlorosulfonic acid (4.75 mL, 71.4 mmol) in a dropwise fashion and the reaction mixture was left to stir at room temperature for 6 h. Upon completion of the reaction, the reaction mixture was poured onto a slurry of ice (15 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were then washed with saturated $NaHCO_3$ (2 × 20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using a combination of ethyl acetate and hexane (1:10) as eluent to provide the corresponding sulfonated derivatives **11**.

4-Propylbenzene-1-sulfonyl chloride (**11a**): colorless oil, 61% (1.58 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, $J = 8.4$ Hz, 2H, Ar), 7.39 (d, $J = 8.4$ Hz, 2H, Ar), 2.69 (t, $J = 7.6$ Hz, 2H, H-1), 1.78–1.42 (m, 2H, H-2), 0.94 (t, $J = 7.4$ Hz, 3H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.2, 141.5, 129.4, 126.8 (Ar), 37.8 (C-1), 23.9 (C-2), 13.5 (C-3). The spectroscopic data were in agreement with the literature report (Imamura et al. 1994).

4-(2-Methylbutyl)benzene-1-sulfonyl chloride (**11b**): colorless oil, 53% (1.24 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.92 (d, $J = 8.0$ Hz, 2H, Ar), 7.36 (d, $J = 8.4$ Hz, 2H, Ar), 2.74 (dd, $J = 6.4$ and 12.4 Hz, 1H, H-1a), 2.47 (dd, $J = 8.4$ and 13.4 Hz, 1H, H-1b), 1.78–1.62 (m, 1H, H-2), 1.49–1.10

(m, 2H, H-3), 1.00–0.61 (m, 6H, H-4, and H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.6, 141.8, 130.3, 126.9 (Ar), 43.3 (C-1), 36.5 (C-2), 29.2 (C-3), 18.8 (C-4 and C-5), 11.4 (C-1). The spectroscopic data were in agreement with the literature report (Katagiri et al. 1989).

4-Hexylbenzene-1-sulfonyl chloride (**11c**): colorless oil, 77% (2.03 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, J = 8.4 Hz, 2H, Ar), 7.41 (d, J = 8.4 Hz, 2H, Ar), 2.73 (t, J = 6.4 Hz, 2H, H-1), 1.68–1.58 (m, 2H, H-2), 1.50–1.21 (m, 6H, H-3, H-4, and H-5), 0.94 (t, J = 6.8 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.6, 128.8, 128.4, 126.0 (Ar), 56.8 (C-1), 32.0 (C-2), 31.5 (C-3), 21.0 (C-4 and C-5), 14.1 (C-6). The spectroscopic data were in agreement with the literature report (Ahad et al. 2011).

4-Octylbenzene-1-sulfonyl chloride (**11d**): colorless oil, 74% (1.33 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.88 (d, J = 8.4 Hz, 2H, Ar), 7.40 (d, J = 8.4 Hz, 2H, Ar), 2.68 (t, J = 7.6 Hz, 2H, H-1), 1.68–1.62 (m, 2H, H-2), 1.35–1.26 (m, 10H, H-3 to H-7), 0.88 (t, J = 7.4 Hz, 3H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.1, 129.0, 128.6, 126.0 (Ar), 56.2 (C-1), 33.2 (C-6), 32.0 (C-2), 31.2 (C-4), 29.9 (C-3), 29.6 (C-5), 22.9 (C-7), 14.3 (C-8). The spectroscopic data were in agreement with the literature report (Ahad et al. 2011).

4-Octadecylbenzene-1-sulfonyl chloride (**11e**)**:** white oil, 63% (1.51 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.91 (d, J = 8.4 Hz, 2H, Ar), 7.40 (d, J = 8.4 Hz, 2H, Ar), 2.71 (t, J = 7.6 Hz, 2H, H-1), 1.74–1.68 (m, 2H, H-2), 1.28–1.20 (m, 30H, H-3 to H-17), 0.88 (t, J = 6.4 Hz, 3H, H-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.0, 142.8, 130.0, 127.3 (Ar), 36.1 (C-1), 32.1 (C-16), 30.8 (C-2), 29.9 (C-3), 29.3 (C-4–15), 29.1, 22.5 (C-17), 14.1 (C-18). The spectroscopic data were in agreement with the literature report (Ahad et al. 2011).

General procedure for the synthesis of arylthiols 12a−e

To a solution of sulfonyl chloride derivative **11** (9.85 mmol) in anhydrous diethyl ether (15 mL) under an atmosphere of nitrogen was added $LiAlH_4$ (0.560 g, 14.8 mmol) in portions. The reaction mixture was then refluxed at 35 °C for 24 h upon which TLC analysis showed reaction completion. The reaction was then cooled on ice and quenched by slow addition of a 10% solution of aqueous Na_2SO_4. The solids were then filtered off and washed several times with hot ethyl acetate. The filtrate was then concentrated under reduced pressure and the crude products thus isolated were purified by silica gel column chromatography using hexane as the eluent to yield the corresponding thiophenols **12**.

4-Propylbenzenethiol (**12a**): colorless oil, 72% (1.50 g), IR (neat cm^{-1}): 2973, 2900, 1608, 1504, 1460, 1154, 1085; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19 (d, J = 8.0 Hz, 2H, Ar), 7.04 (d, J = 8.0 Hz, 2H, Ar), 3.38 (s, 1H, SH), 2.52 (t, J = 7.6 Hz, 2H, H-1), 1.74–1.55 (m, 2H, H-2), 0.91 (t, J = 7.4 Hz, 3H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.5, 129.8, 129.2, 126.8 (Ar), 37.4 (C-1), 24.5 (C-2), 13.7 (C-3). HRMS (ESI): m/z [M − H$^+$] Calcd for $C_9H_{11}S$: 151.0581; found 151.0581.

4-(2-Methylbutyl)benzenethiol (**12b**): colorless oil, 78% (0.68 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18 (d, J = 8.0 Hz, 2H, Ar), 7.00 (d, J = 8.0 Hz, 2H, Ar), 3.37 (s, 1H, SH), 2.62–2.53 (m, 1H, H-1a), 2.38–2.25 (m, 1H, H-1b), 1.68–1.51 (m, 1H, H-2), 1.48–1.32 (m, 1H, H-3a), 1.25–1.08 (m, 1H, H-3b), 0.96–0.78 (m, 6H, H-4, and H-5); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.5, 129.9, 129.7, 128.2 (Ar), 42.7 (C-1), 36.6 (C-2), 29.1 (C-3), 18.9 (C-5), 11.5 (C-4). The spectroscopic data were in agreement with the literature report (Katagiri et al. 1989).

4-Hexylbenzenethiol (**12c**): colorless oil, 83% (1.23 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (d, J = 8.0 Hz, 2H, Ar), 7.01 (d, J = 8.0 Hz, 2H, Ar), 3.39 (s, 1H, SH), 2.55 (t, J = 7.8 Hz, 2H, H-1), 1.68–1.50 (m, 2H, H-2), 1.42–1.20 (m, 6H, H-3, H-4, and H-5), 0.89 (t, J = 6.6 Hz, 3H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.7, 129.8, 129.2, 126.8 (Ar), 35.4 (C-1), 31.7 (C-3), 31.4 (C-2), 28.9 (C-4), 22.6 (C-5), 14.1 (C-6). The spectroscopic data were in agreement with the literature report (Hasegawa et al. 2005).

4-Octylbenzenethiol (**12d**): colorless oil, 71% (0.73 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, J = 7.6 Hz, 2H, Ar), 7.10 (d, J = 8.0 Hz, 2H, Ar), 3.38 (s, 1H, SH), 2.55 (t, J = 7.8 Hz, 2H, H-1), 1.68–1.52 (m, 2H, H-2), 1.42–1.28 (m, 10H, H-3 to H-7), 0.87 (t, J = 6.4 Hz, 3H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.8, 128.9, 128.8, 126.4 (Ar), 36.3 (C-1), 32.3 (C-6), 32.0 (C-4), 31.2(C-2), 29.9 (C-3), 29.6 (C-5), 22.9 (C-7), 14.1 (C-8). The spectroscopic data were in agreement with the literature report. (Hasegawa et al. 2005)

4-Octadecylbenzenethiol (**12e**): white solid, mp 54–56 °C, 73% (0.81 g), IR (neat cm^{-1}): 2970, 2906, 1610, 1503, 1461, 1135, 1015; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20 (d, J = 8.0 Hz, 2H, Ar), 7.06 (d, J = 8.0 Hz, 2H, Ar), 3.38 (s, 1H, SH), 2.56 (t, J = 7.8 Hz, 2H, H-1), 1.60–1.55 (m, 2H, H-2), 1.56–1.20 (m, 30H, H-3 to H-17), 0.88 (t, J = 6.9 Hz, 3H, H-18); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.8, 129.9, 129.2, 126.9 (Ar), 35.6 (C-1), 32.0 (C-16), 31.4 (C-2), 29.9 (C-3–14), 29.8 (C-15), 22.7 (C-17), 14.1 (C-18). HRMS (ESI): m/z [M − H$^+$] calcd for $C_{24}H_{41}S$: 361.2934; found 361.2936.

General procedure for the synthesis of sulfides 14a–e

To a solution of thiophenol **12** (6.44 mmol) in DMF (10 mL), sodium hydride (60% dispersion on oil, 92.7 mg, 6.44 mmol) was added and the mixture was vigorously stirred at room temperature for 10 min under nitrogen. A solution of glycosyl **13** (2.64 g, 4.29 mmol) in DMF (2 mL) was then added and after 5 min of stirring, methanol (3 mL) was

added dropwise and the resulting clear solution was concentrated under reduced pressure. The solution was transferred to silica gel chromatography (ethyl acetate/hexane, 2:8) to give the corresponding sulfide **14**.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(4-propylbenzene)thiomethyl-α and -β-D-glucopyranosyl (**14a**): colorless oil, 94% (2.58 g), IR (neat cm^{-1}): 1750, 1491, 1449, 1091, 680; ^1H NMR (400 MHz, $CDCl_3$) δ: β-anomer 7.43–7.12 (m, 19 H, Ar), 5.67 (d, $J = 8.8$ Hz, 1H, H-1), 4.91 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.78 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.66 (d, $J = 9.4$ Hz, 1H, $-OCH_AH_BPh$), 4.63 (d, $J = 9.4$ Hz, 1H, $-OCH_AH_BPh$), 4.60–4.42 (m, 2H, $-OCH_2Ph$), 3.92–3.54 (m, 5 H, H-3, H-4, H-5, H-6a, and H-6b), 3.26 (dd, $J = 4.2$ and 13.4 Hz, 1H, H-7a), 3.14 (dd, $J = 3.2$ and 13.2 Hz, 1H, H-7b), 2.53 (t, $J = 7.6$ Hz, 2H, $-SArCH_2CH_2CH_3$), 2.32–2.17 (m, 1H, H-2), 1.96 (s, 3H, OAc), 1.70–1.51 (m, 2H, $-SArCH_2CH_2CH_3$), 0.92 (t, $J = 7.2$ Hz, 3H, $-SArCH_2CH_2CH_3$); δ: α-anomer 6.41 (d, $J = 3.2$ Hz, 1H, H-1), 4.95 (d, $J = 11.6$ Hz, 1H, $-OCH_AH_BPh$), 3.41 (dd, $J = 3.4$ and 13.8 Hz, 1H, H-7a), 2.03 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ: β-anomer 168.8 (C=O), 141.4, 138.1, 137.9, 133.3, 129.5, 129.2, 128.5, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6 (Ar), 93.2 (C-1), 80.3 (C-3), 79.0 (C-4), 75.4 (C-5), 75.2 ($-OCH_2Ph$), 74.6 ($-OCH_2Ph$), 73.5 ($-OCH_2Ph$), 68.2 (C-6), 46.2 (C-2), 37.5 ($-SArCH_2CH_2CH_3$), 32.1 (C-7), 24.4 ($-SArCH_2CH_2CH_3$), 20.9 (OAc), 13.8 ($ArCH_2CH_2CH_3$); δ: α-anomer 160.0 (C=O), 137.8, 130.4, 128.4, 128.3, 128.0, 127.8, 127.6 (Ar), 92.0 (C-1), 78.8 (C-3), 75.3 ($-OCH_2Ph$), 74.9 ($-OCH_2Ph$), 44.4 (C-2), 31.3 (C-7). HRMS (ESI): m/z $[M + Na^+]$ calcd for $C_{39}H_{44}NaO_6S$: 663.2751; found: 663.2750.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-[4-(2-methylbutyl)benzene]thiomethyl-α and -β-D-glucopyranosyl (**14b**): colorless oil, 87% (2.20 g), IR (neat cm^{-1}): 1752, 1496, 1455, 1130, 698; ^1H NMR (400 MHz, $CDCl_3$) δ: α-anomer 7.48–7.00 (m, 19H, Ar), 6.39 (d, $J = 2.8$ Hz, 1H, H-1), 4.93 (d, $J = 11.2$ Hz, 1H, $-OCH_AH_BPh$), 4.76 (d, $J = 10.6$ Hz, 1H, $-OCH_AH_BPh$), 4.67 (d, $J = 11.2$ Hz, 1H, $-OCH_AH_BPh$), 4.61 (d, $J = 12.0$ Hz, 1H, $-OCH_AH_BPh$), 4.51 (d, $J = 10.6$ Hz, 1H, $-OCH_AH_BPh$), 4.46 (d, $J = 12.0$ Hz, 1H, $-OCH_AH_BPh$), 3.83–3.50 (m, 6H, H-3, H-4, H-5, H-6a, H-6b, and H-7a), 3.39 (dd, $J = 2.8$ and 13.6 Hz, 1H, H-7b), 2.65–2.42 (m, 1H, $-SArCH_AH_BCHCH_3CH_2CH_3$), 2.38–2.17 (m, 2H, H-2, and $-SArCH_AH_BCHCH_3CH_2CH_3$), 2.03 (s, 3H, OAc), 1.70–1.51 (m, 1H, $-SArCH_2CHCH_3CH_2CH_3$), 1.47–1.10 (m, 2H, $-SArCH_2CHCH_3CH_2CH_3$), 0.94–0.70 (m, 6H, $-SArCH_2CHCH_3CH_2CH_3$). HRMS (ESI): m/z $[M + Na^+]$ calcd for $C_{41}H_{48}NaO_6S$: 691.3064; found: 691.3061.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(4-hexylbenzene)thiomethyl-α and -β-D-glucopyranosyl (**14c**): colorless oil, 86% (1.91 g), IR (neat cm^{-1}): 1753, 1501, 1460, 1131, 699; ^1H NMR (400 MHz, $CDCl_3$) δ: α-anomer 7.48–7.00 (m, 17H, Ar), 5.50 (d, $J = 3.2$ Hz, 1H, H-1), 4.89 (d, $J = 11.2$ Hz, 1H, $-OCH_AH_BPh$), 4.77 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.69–4.45 (m, 4H, the remaining $-OCH_2Ph$), 4.13–4.00 (m, 1H, H-3), 3.80–3.48 (m, 5H, H-4, H-5, H-6a, H-6b, and H-7a), 3.34 (dd, $J = 3.0$ and 13.0 Hz, 1H, H-7b), 2.54 (t, $J = 7.8$ Hz, 2H, $-SArCH_2(CH_2)_4CH_3$), 2.15–2.00 (m, 1H, H-2), 1.98 (s, 3H, OAc), 1.64–1.50 (m, 2H, $-SArCH_2CH_2(CH_2)_3CH_3$), 1.40–1.20 (m, 6H, $-SArCH_2CH_2(CH_2)_3CH_3$), 0.98–0.75 (m, 3H, $-SArCH_2(CH_2)_4CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: α-anomer 160.3 (C=O), 140.8, 138.3, 138.1, 137.8, 132.6, 129.9, 129.1, 128.5, 128.4, 128.0, 127.8, 127.7 (Ar), 92.5 (C-1), 80.2 (C-3), 79.8 (C-4), 75.3 (C-5), 74.8 ($-OCH_2Ph$), 73.5 ($-OCH_2Ph$), 70.8 ($-OCH_2Ph$), 68.9 (C-6), 45.7 (C-2), 35.5 ($-SArCH_2(CH_2)_4CH_3$), 31.7 (C-7), 31.4, 28.9, 22.6 ($-SArCH_2(CH_2)_4CH_3$), 20.1 (OAc), 14.1 ($-SArCH_2(CH_2)_4CH_3$). HRMS (ESI): m/z $[M + Na^+]$ calcd for $C_{42}H_{50}NaO_6S$: 705.3220; found: 705.3218.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(4-octylbenzene)thiomethyl-α and -β-D-glucopyranosyl (**14d**): a colorless oil, 83% (1.64 g), IR (neat cm^{-1}): 1750, 1500, 1460, 1131, 610; ^1H NMR (400 MHz, $CDCl_3$) δ: α-anomer 7.50–7.02 (m, 19H, Ar), 6.40 (bs, 1H, H-1), 4.98 (d, $J = 11.2$ Hz, 1H, $-OCH_AH_BPh$), 4.79 (d, $J = 10.4$ Hz, 1H, $-OCH_AH_BPh$), 4.75–4.42 (m, 4H, the remaining $-OCH_2Ph$), 3.95–3.62 (m, 5H, H-3, H-4, H-5, H-6a, and H-6b), 3.38 (d, $J = 13.2$ Hz, 1H, H-7a), 2.56 (t, $J = 12.4$ Hz, 1H, H-7b), 2.51 (t, $J = 7.8$ Hz, 2H, $-SArCH_2(CH_2)_6CH_3$), 2.95–2.18 (m, 1H, H-2), 2.05 (s, 3H, OAc), 1.63–1.30 (m, 12H, $-SArCH_2(CH_2)_6CH_3$), 0.91 (t, $J = 6.4$ Hz, 3H, $-SArCH_2(CH_2)_6CH_3$); δ: β-anomer 5.68 (d, $J = 8.8$ Hz, 1H, H-1), 3.27 (d, $J = 11.6$ Hz, 1H, H-7a), 3.15 (d, $J = 12.8$ Hz, 1H, H-7b), 2.0 (s, 3H, OAc); ^{13}C NMR (100 MHz, $CDCl_3$) δ: α-anomer 169.0 (C=O), 138.3, 137.9, 137.5, 136.2, 132.0, 130.6, 130.0, 128.4, 128.3, 128.0, 127.8, 127.8 (Ar), 92.1 (C-1), 78.9 (C-4), 78.8 (C-3), 75.4 (C-5), 75.0 ($-OCH_2Ph$), 73.5 ($-OCH_2Ph$), 73.0 ($-OCH_2Ph$), 68.1 (C-6), 44.3 (C-2), 35.6 ($-SArCH_2(CH_2)_6CH_3$), 31.8 ($-SArCH_2CH_2CH_2(CH_2)_4CH_3$), 32.0 ($-SAr(CH_2)_3CH_2CH_2(CH_2)_2CH_3$), 31.4 (C-7), 28.9 ($-SAr(CH_2)_5CH_2CH_2CH_3$), 22.6 ($-SAr(CH_2)_6CH_2CH_3$), 20.9 (OAc), 14.1 ($-SAr(CH_2)_7CH_3$). HRMS (ESI): m/z $[M + Na^+]$ calcd for $C_{44}H_{54}NaO_6S$: 733.3533; found: 733.3530.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(4-octadecylbenzene)thiomethyl-α and -β-D-glucopyranosyl (**14e**): colorless oil, 89% (0.53 g), IR (neat cm^{-1}): 1753, 1650, 1501, 1460, 1131, 1030, 1009, 689; ^1H NMR (400 MHz, $CDCl_3$) δ: *β*-anomer 7.48–7.00 (m, 19 H, Ar), 6.39 (d, $J = 3.2$ Hz, 1H, H-1), 4.93 (d, $J = 11.2$ Hz, 1H, $-OCH_AH_BPh$), 4.76 (d, $J = 10.8$ Hz, 1H $-OCH_AH_BPh$), 4.66 (d, $J = 11.2$ Hz, 1H, $-OCH_AH_BPh$), 4.61 (d, $J = 12.0$ Hz, 1H, $-OCH_AH_BPh$), 4.52 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.46 (d, $J = 12.0$ Hz, 1H, $-OCH_AH_BPh$), 3.82–3.56 (m, 6H,

H-3, H-4, H-5, H-6a, H-6b, and H-7a), 3.38 (dd, $J = 3.2$ and 14.0 Hz, 1H, H-7b), 2.60–2.43 (m, 2H, $-SArC\underline{H}_2(CH_2)_{16}CH_3$), 2.26–2.14 (m, 1H, H-2), 2.01 (s, 3H, OAc), 1.61–1.40 (m, 2H, $-SArCH_2C\underline{H}_2(CH_2)_{15}CH_3$), 1.35–1.10 (m, 30H, $-SArCH_2CH_2(C\underline{H}_2)_{15}CH_3$), 0.86 (t, $J = 6.6$ Hz, 3H, $ArCH_2(CH_2)_{16}C\underline{H}_3$). HRMS (ESI): *m/z* $[M + Na^+]$ calcd for $C_{54}H_{74}NaO_6S$: 873.5098; found: 873.5094.

General procedure for the synthesis of thiochromans 15a–e

Sulfide **14** (2.43 mmol) was dissolved in dry dichloromethane (5 mL) under an atmosphere of nitrogen and stirred together with 4 Å molecular sieves at room temperature for 1 h. The mixture was cooled down to 0 °C and then treated with $BF_3{\cdot}Et_2O$ (1.80 mL of 48% BF_3 solution in diethyl ether, 7.30 mmol) added dropwise. After stirring for 10 min, Et_3N (1 mL) was added and the solids removed by filtration through a Celite bed. The solution was then diluted with water (10 mL) and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phases were successively washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (2 × 10 mL), then dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:9) to yield the corresponding thiochromans **15**.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-propyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (**15a**): white solid, mp 95–100 °C, 88% (1.24 g), $[\alpha]_D$: + 63.0 (c 0.1, $CHCl_3$), IR (neat cm^{-1}): 1450, 1108, 1020, 980, 695; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.50–7.03 (m, 16 H, Ar), 6.97 (d, $J = 8.0$ Hz, 1H, Ar), 6.91 (d, $J = 8.0$ Hz, 1H, Ar), 5.12 (d, $J = 5.6$ Hz, 1H, H-10b), 4.97 (d, $J = 10.3$ Hz, 1H, $-OC\underline{H}_AH_BPh$), 4.89 (d, $J = 11.2$ Hz, 1H, $-OC\underline{H}_AH_BPh$), 4.79 (d, $J = 10.3$ Hz, 1H, $-OCH_A\underline{H}_BPh$), 4.70 (d, $J = 12.0$ Hz, 1H, $-OC\underline{H}_AH_BPh$), 4.64–4.47 (m, 2H, 2 × $-OCH_A\underline{H}_BPh$), 4.06 (t, $J = 9.4$ Hz, 1H, H-4), 3.88–3.70 (m, 3H, H-3, and $-C\underline{H}_2OBn$), 3.61–3.49 (m, 1H, H-2), 3.34 (bd, $J = 13.2$ Hz, 1H, H-5a), 3.19 (bd, $J = 13.2$ Hz, 1H, H-5b), 2.61–3.49 (m, 1H, H-4a), 2.48 (t, $J = 7.4$ Hz, 2H, $-SArC\underline{H}_2CH_2CH_3$), 1.58–1.50 (m, 2H, $-SArCH_2C\underline{H}_2CH_3$), 0.89 (t, $J = 7.2$ Hz, 3H, $-SArCH_2CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.4, 138.7, 138.1, 138.0, 131.0, 130.9, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 126.1 (Ar), 80.2 (C-3), 78.8 (C-4), 75.8 ($-O\underline{C}H_2Ph$), 74.8 ($-O\underline{C}H_2Ph$), 73.4 ($-O\underline{C}H_2Ph$), 72.8 (C-2), 72.5 (C-10b), 69.1 ($-\underline{C}H_2OBn$), 38.6 (C-4a), 37.5 ($-SAr\underline{C}H_2CH_2CH_3$), 26.4 (C-5), 24.5 ($-SArCH_2\underline{C}H_2CH_3$), 13.7 ($-SArCH_2CH_2\underline{C}H_3$). HRMS (ESI): *m/z* $[M + H^+]$ calcd for $C_{37}H_{41}O_4S$: 538.2720; found: 538.2718.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxy)methyl)-9-(2-methylbutyl)-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (**15b**): white solid, mp 85–90 °C, 72% (65 mg), $[\alpha]_D$: + 109.5 (c 0.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.11 (m, 13H, Ar), 7.06–6.99 (m, 3H, Ar), 6.89 (d, $J = 8.0$ Hz, 1H, Ar), 6.81 (d, $J = 8.0$ Hz, 1H, Ar), 5.06 (d, $J = 5.6$ Hz, 1H, H-10b), 4.90 (d, $J = 10.8$ Hz, 1H, $-OC\underline{H}_AH_BPh$), 4.80 (d, $J = 11.2$ Hz, 1H, $-OC\underline{H}_AH_BPh$), 4.71 (d, $J = 10.8$ Hz, 1H, $-OCH_A\underline{H}_BPh$), 4.63 (d, $J = 12.4$ Hz, 1H, $-OC\underline{H}_AH_BPh$), 4.52–4.40 (m, 2H, 2 × $-OCH_A\underline{H}_BPh$), 4.00 (t, $J = 9.8$ Hz, 1H, H-4), 3.74–3.61 (m, 3H, H-3, and $-C\underline{H}_2OBn$), 3.42 (bd, $J = 9.6$ Hz, 1H, H-2), 3.27 (bd, $J = 13.6$ Hz, 1H, H-5a), 3.11 (dd, $J = 4.0$ and 13.2 Hz, 1H, H-5b), 2.51–2.38 (m, 2H, $-SArC\underline{H}_2CHCH_3CH_2CH_3$), 2.24–2.16 (m, 1H, H-4a), 1.56–1.42 (m, 1H, $-SArCH_2C\underline{H}CH_3CH_2CH_3$), 1.32–1.21 (m, 1H, $-SArCH_2CHCH_3C\underline{H}_AH_BCH_3$), 1.11–0.98 (m, 1H, $-SArCH_2CHCH_3CH_A\underline{H}_BCH_3$), 0.86–0.75 (m, 3H, $-SArCH_2CHC\underline{H}_3CH_2CH_3$), 0.73 (t, $J = 5.8$ Hz, 3H, $-SArCH_2CHCH_3CH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.8, 138.4, 138.1, 138.0, 131.0, 130.9, 128.7, 128.5, 128.4, 128.3, 127.9, 127.7, 127.6, 126.0 (Ar), 80.2 (C-3), 78.9 (C-4), 75.9 ($-O\underline{C}H_2Ph$), 74.9 ($-O\underline{C}H_2Ph$), 73.5 ($-O\underline{C}H_2Ph$), 72.9 (C-2), 72.5 (C-10b), 69.1 ($-\underline{C}H_2OBn$), 42.8 ($-SAr\underline{C}H_2CHCH_3CH_2CH_3$), 38.7 (C-4a), 36.6 ($-SArCH_2\underline{C}HCH_3CH_2CH_3$), 28.9 ($-SArCH_2CHCH_3\underline{C}H_2CH_3$), 26.5 (C-5), 18.9 ($-SArCH_2CH\underline{C}H_3CH_2CH_3$), 11.5 ($-SArCH_2CHCH_3CH_2\underline{C}H_3$). HRMS (ESI): *m/z* $[M + H^+]$ calcd for $C_{39}H_{45}O_4S$: 609.3039; found: 609.3025.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-hexyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (**15c**): white solid, mp 90–93 °C, 78% (1.32 g), IR (neat cm^{-1}): 1470, 1134, 1103, 1023, 697; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.38–6.82 (m, 18H, Ar), 5.05 (d, $J = 5.6$ Hz, 1H, H-10b), 4.86 (d, $J = 10.8$ Hz, 1H, $-OC\underline{H}_AH_BPh$), 4.80 (d, $J = 10.8$ Hz, 1H, $-OCH_A\underline{H}_BPh$), 4.72 (d, $J = 10.4$ Hz, 1H, $-OC\underline{H}_AH_BPh$), 4.63 (d, $J = 12.2$ Hz, 1H, $-OC\underline{H}_AH_BPh$), 4.48 (d, $J = 12.2$ Hz, 1H, $-OCH_A\underline{H}_BPh$), 4.44 (d, $J = 10.4$ Hz, 1H, $-OCH_A\underline{H}_BPh$), 3.98 (t, $J = 9.8$ Hz, 1H, H-4), 3.77–3.64 (m, 3H, H-3, and $-C\underline{H}_2OBn$), 3.45 (bd, $J = 9.6$ Hz, 1H, H-2), 3.27 (dd, $J = 2.0$ and 13.4 Hz, 1H, H-5a), 3.11 (dd, $J = 3.6$ and 13.4 Hz, 1H, H-5b), 2.58–2.89 (m, 3H, H-4a, and $-SArC\underline{H}_2(CH_2)_4CH_3$), 1.54–1.47 (m, 2H, $-SArCH_2C\underline{H}_2(CH_2)_3CH_3$), 1.31–1.12 (m, 6H, $-SArCH_2CH_2(C\underline{H}_2)_3CH_3$), 0.80 (t, $J = 6.8$ Hz, 3H, $-SArCH_2(CH_2)_4C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.7, 138.8, 138.1, 138.0, 131.1, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 126.2 (Ar), 80.2 (C-3), 78.8 (C-4), 75.9 ($-O\underline{C}H_2Ph$), 74.8 ($-O\underline{C}H_2Ph$), 73.5 ($-O\underline{C}H_2Ph$), 72.9 (C-2), 72.5 (C-10b), 69.1 ($-\underline{C}H_2OBn$), 38.7 (C-4a), 35.5 ($-SAr\underline{C}H_2(CH_2)_4CH_3$), 31.7 ($-SArCH_2\underline{C}H_2(CH_2)_3CH_3$), 31.5 ($-SAr(CH_2)_2\underline{C}H_2(CH_2)_2CH_3$), 28.9 ($-SAr(CH_2)_3\underline{C}H_2CH_2CH_3$), 26.4 (C-5), 22.6 ($-SAr(CH_2)_4\underline{C}H_2CH_3$), 14.1 ($-SAr(CH_2)_5\underline{C}H_3$). HRMS (ESI): *m/*

z $[M + H^+]$ calcd for $C_{40}H_{47}O_4S$: 623.3190; found: 623.3190.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-octyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (**15d**): white solid, mp 88–90 °C, 81% (1.33 g), IR (neat cm^{-1}): 1473, 1130, 1100, 1040, 1020, 697; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.50–6.81 (m, 18H, Ar), 5.11 (d, $J = 4.8$ Hz, 1H, H-10b), 4.96 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.86 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.78 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.70 (d, $J = 12.0$ Hz, 1H, $-OCH_AH_BPh$), 4.61–4.42 (m, 2H, $2 \times -OCH_AH_B$ Ph), 4.05 (t, $J = 9.6$ Hz, 1H, H-4), 3.88–3.67 (m, 3H, H-3, and $-CH_2OBn$), 3.60–3.45 (m, 1H, H-2), 3.33 (bd, $J = 13.4$ Hz, 1H, H-5a), 3.18 (dd, $J = 3.4$ and 13.4 Hz, 1H, H-5b), 2.61–2.53 (m, 2H, $-SArCH_2(CH_2)_6CH_3$), 2.31–2.15 (m, 2H, $-SArCH_2CH_2(CH_2)_5CH_3$), 1.55–1.43 (m, 2H, $-SAr(CH_2)_2CH_2(CH_2)_4CH_3$), 1.39–1.14 (m, 8H, $-SAr(CH_2)_3(CH_2)_4CH_3$), 0.86 (t, $J = 7.2$ Hz, 3H, $-SArCH_2(CH_2)_6CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.7, 138.8, 138.1, 138.0, 131.1, 130.8, 128.5, 128.4, 128.0, 127.8, 127.7, 127.6, 127.5, 126.2 (Ar), 80.2 (C-3), 78.8 (C-4), 75.9 ($-OCH_2Ph$), 74.8 ($-OCH_2Ph$), 73.4 ($-OCH_2Ph$), 72.8 (C-2), 72.5 (C-10b), 69.1 ($-CH_2OBn$), 38.7 (C-4a), 35.5 ($-SArCH_2(CH_2)_6CH_3$), 31.9, 31.5, 29.5, 29.3, 29.2 ($-SArCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$), 26.4 (C-5), 22.7 ($-SAr(CH_2)_6CH_2CH_3$), 14.1 ($-SAr(CH_2)_7CH_3$). HRMS (ESI): m/z $[M + H^+]$ calcd for $C_{42}H_{51}O_4S$: 651.3503; found: 651.3502.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-octadecyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (**15e**): white solid, mp 125–130 °C, 68% (0.35 g), $[\alpha]_D$: +93.0 (c 0.1, $CHCl_3$), IR (neat cm^{-1}): 1496, 1406, 1123, 1140, 1035, 694; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.45–7.06 (m, 16H, Ar), 6.95 (d, $J = 8.0$ Hz, 1H, Ar), 6.91 (d, $J = 1.6$ Hz, 1H, Ar), 5.11 (d, $J = 5.6$ Hz, 1H, H-10b), 4.95 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.86 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.77 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.67 (d, $J = 12.0$ Hz, 1H, $-OCH_AH_BPh$), 4.54 (d, $J = 12.0$ Hz, 1H, $-OCH_AH_BPh$), 4.50 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.02 (t, $J = 10.4$ Hz, 1H, H-4), 3.82–3.65 (m, 3H, H-3, and $-CH_2OBn$), 3.55–3.43 (m, 1H, H-2), 3.33 (dd, $J = 2.2$ and 13.3 Hz, 1H, H-5a), 3.17 (dd, $J = 4.0$ and 13.3 Hz, 1H, H-5b), 2.62–2.40 (m, 3H, H-4, and $-SArCH_2(CH_2)_{16}CH_3$), 1.63–1.43 (m, 2H, $-SArCH_2CH_2(CH_2)_{15}CH_3$), 1.40–1.13 (m, 30H, $-SArCH_2CH_2(CH_2)_{15}CH_3$), 0.86 (t, $J = 6.8$ Hz, 3H, $-SArCH_2(CH_2)_{16}CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 139.7, 138.8, 138.1, 131.1, 130.8, 128.5, 128.4, 127.8, 127.7, 127.5, 126.2 (Ar), 80.2 (C-3), 78.9 (C-4), 75.9 ($-OCH_2Ph$), 74.8 ($-OCH_2Ph$), 73.5 ($-OCH_2Ph$), 72.8 (C-2), 72.5 (C-10b), 69.1 ($-CH_2OBn$), 38.7 (C-4a), 35.5 ($-SArCH_2(CH_2)_{16}CH_3$), 31.9, 31.6, 29.7, 29.6, 29.5, 29.4, 29.3 (overlapping signals of $-SArCH_2(CH_2)_{16}CH_3$), 26.4 (C-5), 22.7 ($-SAr(CH_2)_{16}CH_2CH_3$), 14.1 ($ArCH_2(CH_2)_{16}CH_3$). HRMS (ESI): m/z $[M + H^+]$ calcd for $C_{52}H_{71}O_4S$: 791.5068; found: 791.5061.

General procedure for the oxidation of thiochromans to their sulfone derivatives 16a–e

To a solution of sulfide **15** (1.74 mmol) in dichloromethane (10 mL) was added to a suspension of wet alumina (1.00 g wetted with 100 µL of water) and OXONE® (0.530 g, 3.48 mmol) and the reaction mixture was vigorously stirred overnight at room temperature. The reaction mixture was then filtered to remove the adsorbent. Evaporation of the solvent and flash-chromatographic purification on silica gel (ethyl acetate/petroleum ether, 2:8) gave sulfones **16**.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-propyl-2,3,4,4a,5,10b-hexahydro-*S,S*-dioxothiochromeno[4,3-*b*]pyran (**16a**): colorless oil, 78% (0.83 g); $[\alpha]_D$: +51.5 (c 0.1, $CHCl_3$), IR (neat cm^{-1}): 1455, 1301, 1113, 754, 695; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.82 (d, $J = 8.0$ Hz, 1H, Ar), 7.50–7.12 (m, 17 H, Ar), 5.16 (d, $J = 4.8$ Hz, 1H, H-10b), 4.87 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.80 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.72 (d, $J = 11.2$ Hz, 1H, $-OCH_AH_BPh$), 4.65 (d, $J = 12.0$ Hz, 1H, $-OCH_AH_BPh$), 4.61–4.50 (m, 2H, $2 \times -OCH_AH_B$Ph), 4.15–3.94 (m, 2H, H-4, and H-5a), 3.98–3.62 (m, 4H, H-3, H-2, and $-CH_2OBn$), 3.39 (dd, $J = 3.6$ and 14.4 Hz, 1H, H-5b), 2.98–2.80 (m, 1H, H-4a), 2.39 (t, $J = 7.4$ Hz, 2H, $-SArCH_2CH_2CH_3$), 1.71–1.50 (m, 2H, $-SArCH_2CH_2CH_3$), 0.91 (t, $J = 7.2$ Hz, 3H, $-SArCH_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.4, 138.1, 137.9, 137.6, 136.7, 133.8, 129.7, 128.5, 128.4, 128.0, 127.9, 127.8, 127.6, 123.7 (Ar), 78.4 (C-3), 77.3 (C-4), 74.6 (C-2), 74.3 ($-OCH_2Ph$), 74.1 ($-OCH_2Ph$), 73.4 ($-OCH_2Ph$), 69.6 (C-10b), 68.4 ($-CH_2OBn$), 49.4 (C-5), 39.7 (C-4a), 37.9 ($-SArCH_2CH_2CH_3$), 24.1 ($-SArCH_2CH_2CH_3$), 13.7 ($-SArCH_2CH_2CH_3$). HRMS (ESI): m/z $[M + H^+]$ calcd for $C_{37}H_{41}O_6S$: 613.2637; found: 613.2637.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-(2-methylbutyl)-2,3,4,4a,5,10b-hexahydro-*S,S*-dioxothiochromeno[4,3-*b*]pyran (**16b**): white solid, mp 90–92 °C, 63% (0.87 g), $[\alpha]_D$: +20.0 (c 0.1, $CHCl_3$), IR (neat cm^{-1}): 1454, 1301, 1150, 734, 701; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.75 (d, $J = 8.0$ Hz, 1H, Ar), 7.40–7.15 (m, 17H, Ar), 5.46 (d, $J = 4.8$ Hz, 1H, H-10b), 4.80 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.73 (d, $J = 10.8$ Hz, 1H, $-OCH_AH_BPh$), 4.64 (d, $J = 11.2$ Hz, 1H, $-OCH_AH_BPh$), 4.58 (d, $J = 12.0$ Hz, 1H, $-OCH_AH_BPh$), 4.55–4.45 (m, 2H, $2 \times -OCH_AH_B$Ph), 4.06–3.91 (m, 2H, H-4, and H-5a), 3.84–3.56 (m, 4H, H-3, H-2, and $-CH_2OBn$), 3.32 (dd, $J = 3.4$ and 14.2 Hz, 1H, H-5b), 2.88–2.74 (m, 1H, $-SArCH_AH_BCHCH_3CH_2CH_3$), 2.63–2.55 (m, 1H, $-SArCH_AH_BCHCH_3CH_2CH_3$), 2.40–2.38 (m, 1H, H-4a), 1.62–1.50 (m, 1H, $-SArCH_2CHCH_3CH_2CH_3$), 1.48–1.05

(m, 2H, –SArCH$_2$CHCH$_3$CH$_2$CH$_3$), 0.90–0.68 (m, 6H, –SArCH$_2$CHCH$_3$CH$_2$CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.6, 138.2, 137.9, 137.7, 136.8, 133.7, 130.4, 128.8, 128.5, 128.4, 127.9, 127.8, 127.7, 123.6 (Ar), 78.4 (C-3), 77.3 (C-4), 74.4 (–OCH$_2$Ph), 74.1 (C-2 and –OCH$_2$Ph), 73.5 (–OCH$_2$Ph), 69.5 (C-10b), 68.4 (–CH$_2$OBn), 49.5 (C-5), 43.4 (–SArCH$_2$CHCH$_3$CH$_2$CH$_3$), 39.9 (C-4a), 36.4 (–SArCH$_2$CHCH$_3$CH$_2$CH$_3$), 29.2 (–SArCH$_2$CHCH$_3$CH$_2$CH$_3$), 18.9 (–SArCH$_2$CHCH$_3$CH$_2$CH$_3$), 11.3 (–SArCH$_2$CHCH$_3$CH$_2$CH$_3$). HRMS (ESI): *m/z* [M + H$^+$] calcd for $C_{39}H_{44}NaO_6S$: 641.2937; found: 641.2907.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-hexyl-2,3,4,4a,5,10b-hexahydro-*S,S*-dioxothiochromeno[4,3-*b*]pyran (**16c**): colorless oil, 71% (0.93 g), IR (neat cm^{-1}): 1456, 1300, 1103, 984. 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (d, J = 8.0 Hz, 1H, Ar), 7.40–7.13 (m, 17H, Ar), 5.08 (d, J = 5.6 Hz, 1H, H-10b), 4.84 (d, J = 10.8 Hz, 1H, –OCH$_A$H$_B$Ph), 4.82 (d, J = 10.8 Hz, 1H, –OCH$_A$H$_B$Ph), 4.72 (d, J = 10.4 Hz, 1H, –OCH$_A$H$_B$Ph), 4.63 (d, J = 12.2 Hz, 1H, –OCH$_A$H$_B$Ph), 4.48 (d, J = 12.2 Hz, 1H, –OCH$_A$H$_B$Ph), 4.44 (d, J = 10.4 Hz, 1H, –OCH$_A$H$_B$Ph), 4.01–3.90 (m, 2H, H-4, and H-5a), 3.82–3.55 (m, 4H, H-3, H-2, and –CH$_2$OBn), 3.32 (dd, J = 3.2 and 14.0 Hz, 1H, H-5b), 2.86–2.61 (m, 1H, H-4a), 2.52 (t, J = 7.4 Hz, 2H, –SArCH$_2$(CH$_2$)$_4$CH$_3$), 1.54–1.47 (m, 2H, –SArCH$_2$CH$_2$(CH$_2$)$_3$CH$_3$), 1.31–1.12 (m, 6H, –SArCH$_2$CH$_2$(CH$_2$)$_3$CH$_3$), 0.80 (t, J = 6.8 Hz, 3H, –SArCH$_2$(CH$_2$)$_4$CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.7, 138.8, 138.1, 138.0, 131.1, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 126.2 (Ar), 78.9 (C-3), 77.5 (C-4), 75.8 (–OCH$_2$Ph), 74.8 (–OCH$_2$Ph), 73.4 (–OCH$_2$Ph), 73.0 (C-2), 70.0 (C-10b), 68.8 (–CH$_2$OBn), 49.3 (C-5), 42.3 (–SArCH$_2$(CH$_2$)$_4$CH$_3$), 39.8 (C-4a), 31.6 (–SArCH$_2$CH$_2$(CH$_2$)$_3$CH$_3$), 31.4 (–SAr(CH$_2$)$_2$CH$_2$(CH$_2$)$_2$CH$_3$), 28.9 (–SAr(CH$_2$)$_3$CH$_2$CH$_2$CH$_3$), 22.6 (–SAr(CH$_2$)$_4$CH$_2$CH$_3$), 14.1 (–SArCH$_2$(CH$_2$)$_4$CH$_3$). HRMS (ESI): *m/z* [M + Na$^+$] calcd for $C_{40}H_{46}NaO_6S$: 677.2907; found: 677.2910.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-octyl-2,3,4,4a,5,10b-hexahydro-*S,S*-dioxothiochromeno[4,3-*b*]pyran (**16d**): colorless oil, 78% (1.15 g), IR (neat cm^{-1}): 1460, 1310, 1109, 1003, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.71 (d, J = 8.0 Hz, 1H, Ar), 7.38–7.00 (m, 17H, Ar), 5.05 (d, J = 4.8 Hz, 1H, H-10b), 4.76 (d, J = 10.8 Hz, 1H, –OCH$_A$H$_B$Ph), 4.69 (d, J = 10.8 Hz, 1H, –OCH$_A$H$_B$Ph), 4.61 (d, J = 11.2 Hz, 1H, –OCH$_A$H$_B$Ph), 4.55 (d, J = 12.0 Hz, 1H, –OCH$_A$H$_B$Ph), 4.50–4.39 (m, 2H, 2 × –OCH$_A$H$_B$Ph), 4.00–3.88 (m, 2H, H-4, and H-5a), 3.68–3.50 (m, 4H, H-3, H-2, and –CH$_2$OBn), 3.32 (dd, J = 3.4 and 14.2 Hz, 1H, H-5b), 2.85–2.60 (m, 1H, H-4a), 2.51 (t, J = 7.4 Hz, 2H, –SArCH$_2$(CH$_2$)$_6$CH$_3$), 1.60–1.41 (m, 2H, –SArCH$_2$CH$_2$(CH$_2$)$_5$CH$_3$), 1.28–1.02 (m, 10 H, –SArCH$_2$CH$_2$(CH$_2$)$_5$CH$_3$), 0.77 (t, J = 6.6 Hz, 3H, –SArCH$_2$(CH$_2$)$_6$CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.7, 138.2, 137.9, 137.6, 136.7, 133.8, 129.7, 128.5, 128.4, 128.0, 127.9, 127.8, 127.6, 123.7 (Ar), 78.4 (C-3), 77.6 (C-4), 74.3 (C-2), 74.1 (–OCH$_2$Ph), 74.0 (–OCH$_2$Ph), 73.5 (–OCH$_2$Ph), 69.6 (C-10b), 68.5 (–CH$_2$OBn), 49.5 (C-5), 39.7 (C-4a), 36.0 (–SArCH$_2$(CH$_2$)$_6$CH$_3$), 31.8, 31.1, 29.4, 29.4, 29.2, 22.6 (–SArCH$_2$(CH$_2$)$_6$CH$_3$), 14.1 (–SArCH$_2$(CH$_2$)$_6$CH$_3$). HRMS (ESI): *m/z* [M + H$^+$] calcd for $C_{42}H_{50}O_6S$: 682.5999; found: 682.6014.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-octadecyl-2,3,4,4a,5,10b-hexahydro-*S,S*-dioxothiochromeno[4,3-*b*]pyran (**16e**): white solid, mp 95–97 °C, 67% (0.98 g), [α]$_D$: +40.0 (c 0.1, $CHCl_3$), IR (neat cm^{-1}): 1455, 1300, 1105.4, 754, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (d, J = 8.0 Hz, 1H, Ar), 7.44–7.08 (m, 17H, Ar), 5.13 (d, J = 4.4 Hz, 1H, H-10b), 4.90 (d, J = 10.6 Hz, 1H, –OCH$_A$H$_B$Ph), 4.83 (d, J = 10.6 Hz, 1H, –OCH$_A$H$_B$Ph). 4.74 (d, J = 11.2 Hz, 1H, –OCH$_A$H$_B$Ph), 4.66 (d, J = 12.0 Hz, 1H, –OCH$_A$H$_B$Ph), 4.62–4.48 (m, 2H, 2 × OCH$_A$H$_B$Ph), 4.14–3.99 (m, 2H, H-4, and H-5a), 3.79–3.65 (m, 4 H, H-3, H-2, and –CH$_2$OBn), 3.17 (dd, J = 4.0 and 13.3 Hz, 1H, H-5b), 2.80–2.61 (m, 1H, H-4a), 2.52 (t, J = 7.4 Hz, 2H, –SArCH$_2$(CH$_2$)$_{16}$CH$_3$), 1.63–1.43 (m, 2H, –SArCH$_2$CH$_2$(CH$_2$)$_{15}$CH$_3$), 1.40–1.13 (m, 30H, –SArCH$_2$CH$_2$(CH$_2$)$_{15}$CH$_3$), 0.86 (t, J = 6.8 Hz, 3H, –SArCH$_2$(CH$_2$)$_{16}$CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.9, 138.4, 137.9, 131.1, 130.4, 129.0, 128.8, 127.8, 126.4, 125.4, 123.6 (Ar), 78.2 (C-3), 77.2 (C-4), 75.9 (–OCH$_2$Ph), 74.8 (–OCH$_2$Ph), 73.5 (–OCH$_2$Ph), 72.8 (C-2), 69.8 (C-10b), 68.3 (–CH$_2$OBn), 49.6 (C-5), 38.7 (C-4a), 36.8 (–SArCH$_2$(CH$_2$)$_{16}$CH$_3$), 31.9, 31.6, 29.7, 29.6, 29.5, 29.4, 29.3, 26.4, 22.7 (overlapping signals of –SArCH$_2$(CH$_2$)$_{16}$CH$_3$), 14.1 (–SArCH$_2$(CH$_2$)$_{16}$CH$_3$). HRMS (ESI): *m/z* [M + Na$^+$] calcd for $C_{52}H_{71}NaO_6S$: 823.4966; found: 823.4971.

3,4,6-Tri-*O*-methyl-1,5-anhydro-2-deoxy-1,2-*C*-dichloromethylene-D-glycero-D-gulo-hexitol (**19**): Benzyltriethylammonium chloride (71.9 mg, 0.320 mmol) was added to a stirring solution of tri-*O*-methyl glucal **18** (2.60 g, 13.8 mmol) dissolved in chloroform (36 mL). Fifty percent aqueous NaOH (36 mL) was then added and the reaction was stirred at 35 °C for 18 h to completion. The reaction mixture was then quenched by adding water (15 mL) and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue product was purified by column chromatography on silica gel using hexane and ethyl acetate (9:1) as eluent to provide the title compound **19**: colorless oil, 70% (2.63 g), [α]$_D$: +41.0 (c 0.1, $CHCl_3$), IR (neat cm^{-1}): 1614, 1560, 1250, 1079, 819; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.86 (d, J = 8.0 Hz, 1H, H-1), 3.78–3.70 (m, 1H, H-4), 3.58–3.28 (m, 13H, H-3, H-5, H-6a, H-6b and 3 × –OCH$_3$), 1.67 (dd, J = 4.4 and 8.0 Hz, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 79.3 (C-4), 78.8

(C-3), 77.4 (C-5), 73.0 (C-6), 61.4 (C-7), 60.1 (–OCH_3), 59.3 (–OCH_3), 58.7 (C-1), 57.1 (–OCH_3), 33.6 (C-2). HRMS (ESI): *m/z* [M + H^+] calcd for $C_{10}H_{20}Cl_2NO_4$ 271.0504; found: 271.0495.

3,4,6-Tri-*O*-methyl-1,5-anhydro-2-deoxy-1,2-*C*-methylene-D-glycero-D-gulo-hexitol (**20**): The dichlororinated cyclopropane **19** (2.23 g, 8.22 mmol) was dissolved in THF (15 mL) under an atmosphere of nitrogen. To this was added lithium aluminum hydride (0.540 g, 14.2 mmol) and the mixture was stirred vigorously for 48 h at room temperature. Upon completion, the reaction was then cooled on ice and quenched by slow addition of 10% aqueous $Na_2SO_4{\cdot}10H_2O$ (15 mL). The formed solids were washed with hot ethyl acetate and the solvent was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure and the product used without further purification: colorless syrup, 76% (2.01 g), $[\alpha]_D$: +29.0 (c 0.1, $CHCl_3$). HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{12}H_{22}IO_6$ 225.1103; found: 225.1092.

1-*O*-Acetyl-3,4–6-tri-*O*-methyl-2-deoxy-2-*C*-iodomethyl-α and β-D-glucopyranoses (**21**): Cyclopropanated sugar **20** (1.90 g, 9.39 mmol) was dissolved in a solution of acetonitrile (5 mL) and acetic acid (3 mL) and cooled on ice. Acetic anhydride (2.66 mL, 28.2 mmol), NH_4I (1.52 g, 10.5 mmol), and 30% H_2O_2 (0.990 mL, 12.7 mmol) were successively added and the reaction was stirred on ice for 10 min and then a further 1 h at room temperature. The mixture was diluted with dichloromethane (10 mL) and washed with a 10% solution of $Na_2S_2O_3$ (10 mL). The aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic fractions were washed with saturated $NaHCO_3$ (2 × 10.0 mL) and brine (10 mL). The organic layer was then dried over anhydrous $MgSO_4$ and removed under reduced pressure. The residue was purified by column chromatography on silica gel using hexane and ethyl acetate (9:1) as eluent to afford **21**: colorless oil, 76% (2.13 g), IR (neat cm^{-1}): 1750, 1228, 1030, 1026, 954, 735, 695.3; ^1H NMR (400 MHz, $CDCl_3$) *δ*: α-anomer 6.24 (d, *J* = 3.2 Hz, 1H, H-1), 3.58–3.24 (m, 14H, H-4, H-5, H-6a, H-6b, H-7a, and 3 × –OCH_3), 3.25–3.18 (m, 1H, H-3), 2.86 (t, *J* = 10.4 Hz, 1H, H-7b), 2.10–2.00 (m, 4H, H-2, and OAc); *δ*: β-anomer 5.48 (d, *J* = 8.8 Hz, 1H, H-1), 3.70–3.15 (m, 15 H, H-4, H-5, H-6a, H-6b, H-7a, H-7b, and 3 × –OCH_3), 2.13–2.00 (m, 4H, H-2, and OAc); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: α-anomer 168.9 (C=O), 93.6 (C-1), 82.8 (C-3), 79.9 (C-4), 73.1 (C-5), 70.6 (C-6), 60.9 (–OCH_3), 60.4 (–OCH_3), 59.3 (–OCH_3), 46.8 (C-2); *δ*: β-anomer 168.9 (C=O), 94.9 (C-1), 82.7 (C-3), 80.3 (C-4), 75.3 (C-5), 70.4 (C-6), 61.1 (–OCH_3), 60.2 (–OCH_3), 59.2 (–OCH_3), 44.9 (C-2), 21.0 (OAc), 4.05 (C-7). HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{12}H_{22}IO_6$ 411.0281; found: 411.0273.

1-*O*-Acetyl-3,4,6-tri-*O*-methyl-2-deoxy-2-*C*-(4-*tert*-butylbenzene)thiomethyl-α and -β-D-glucopyranosyl (**22**): 4-*tert*-Butylbenzenethiol (0.430 mL, 2.48 mmol) was added to DMF (5 mL) under anhydrous conditions and NaH (60% dispersion, 0.100 g, 2.48 mmol) was added. The reaction mixture was left to stir until bubbling ceased. Iodomethyl glycosyl **21** (0.860 g, 2.22 mmol) was then added and the reaction mixture was left with continued stirring under anhydrous conditions for a further 15 min upon which the reaction showed completion on TLC. Methanol (2 mL) was added in a dropwise fashion until the solution became clear and the solvents were removed under reduced pressure. The resultant residue was purified by column chromatography on silica gel using hexane and ethyl acetate (5:1) as eluent to afford **22**: colorless oil, 86% (0.81 g); $[\alpha]_D$: +51.0 (c 0.1, $CHCl_3$), IR (neat cm^{-1}): 1753, 1530, 1438, 1091, 670; ^1H NMR (400 MHz, $CDCl_3$) *δ*: α-anomer 7.32–7.20 (m, 4H, Ar), 6.32 (d, *J* = 3.2 Hz, 1H, H-1), 3.62–3.24 (m, 15H, H-3, H-4, H-5, H-6a, H-6b, H-7a, and 3 × –OCH_3), 2.58 (dd, *J* = 10.8 and 13.6 Hz, 1H, H-7b), 2.13–2.00 (m, 4H, H-2, and OAc), 1.28 (s, 9H, –SArC($C\underline{H}_3$)$_3$); *δ*: β-anomer 7.32–7.20 (m, 4 H, Ar), 5.57 (d, *J* = 9.2 Hz, 1H, H-1), 3.61–3.28 (m, 14H, H-3, H-4, H-5, H-6a, H-6b, and 3 × –OCH_3), 3.23 (dd, *J* = 4.2 and 13.4 Hz, 1H, H-7a), 3.10 (dd, *J* = 3.4 and 13.4 Hz, 1H, H-7b), 2.10–2.00 (m, 1H, H-2), 1.90 (s, 3H, OAc), 1.27 (s, 9H, –SArC($C\underline{H}_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: β-anomer 169.1 (C=O), 149.7, 132.1, 129.5, 126.1 (Ar), 92.0 (C-1), 82.3 (C-4), 80.2 (C-3), 72.8 (C-5), 70.6 (C-6), 61.0 (–OCH_3), 60.4 (–OCH_3), 59.1 (–OCH_3), 44.1 (C-2), 34.4 (–SAr$\underline{C}$(CH_3)$_3$), 31.3 (–SArC($\underline{C}H_3$)$_3$), 31.2 (C-7), 20.9 (OAc). HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{22}H_{34}NaO_6S$ 449.1974; found: 449.1968.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-9-(*tert*-butyl)-3,4-dimethoxy-2-(methoxymethyl)-2,3,4,4a,5,10b-hexahydrothiochromeno [4,3-*b*]pyran (**23**): Sulfide **22** (0.540 g, 1.27 mmol) was dissolved in dry dichloromethane (3 mL) under an atmosphere of nitrogen and stirred together with 4 Å molecular sieves at room temperature for 1 h. The mixture was cooled down to 0 °C and then $BF_3{\cdot}Et_2O$ (0.94 mL, 7.6 mmol) was added dropwise. After stirring at this temperature for 5 min, Et_3N (0.7 mL) was added and the solids removed by filtration through a pad of Celite®. The solution was then diluted with water (10 mL) and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic phases were successively washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 3:7) to yield the corresponding thiochroman **23**: colorless solid, mp 68–72 °C, 88% (0.41 g), $[\alpha]_D$: +64.5 (c 0.1, $CHCl_3$), IR (neat cm^{-1}): 1481, 1304, 1113, 1012, 699; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 7.56 (d, *J* = 0.8 Hz, 1H, Ar), 7.10 (dd, *J* = 1.6 and 8.4 Hz, 1H, Ar), 6.96 (d, *J* = 8.4 Hz, 1H, Ar), 5.05 (d, *J* = 6.0 Hz, 1H, H-10b), 3.61–3.53 (m, 6 H, H-4, –$C\underline{H}_2OCH_3$, and –OCH_3), 3.50 (s, 3H, –OCH_3), 3.42 (s, 3H, –OCH_3), 3.36–3.24 (m, 3H, H-3, H-2, and H-

5b), 3.11 (dd, $J = 4.0$ and 13.2 Hz, 1H, H-5a), 2.43–2.33 (m, 1H, H-4a), 1.24 (s, 9H, –SArC($C\underline{H}_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.9, 130.8, 130.7, 125.9, 124.7, 124.5 (Ar), 81.9 (C-3), 79.8 (C-4), 72.6 (C-10b), 72.6 (C-2), 71.4 (–$\underline{C}H_2OCH_3$), 61.2 (–OCH_3), 60.2 (–OCH_3), 59.2 (–OCH_3), 38.4 (C-4a), 34.4 (–SAr$\underline{C}$(CH_3)$_3$), 31.2 (–SArC($\underline{C}H_3$)$_3$), 26.1 (C-5). HRMS (ESI): *m/z* [M + Na^+] calcd for $C_{20}H_{30}NaO_4S$ 367.1943; found: 367.1942.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-9-(*tert*-butyl)-3,4-dimethoxy-2-(methoxymethyl)-2,3,4,4a,5,10b-hexahydrothiochromeno [4,3-*b*]pyran *S,S*-dioxide (**24**): Sulfide **23** (0.35 g, 0.95 mmol) was added to a vigorously stirring suspension of wet alumina (2.8 g wetted with 0.31 mL of water) and OXONE® (0.58 g, 3.8 mmol) in dichloromethane (5 mL). The reaction mixture was stirred at room temperature for 12 h. The reaction mixture was then filtered to remove the adsorbent. Evaporation of the solvent and flash chromatographic purification on silica gel (ethyl acetate/hexane, 3:7) afforded the title sulfone **24**: colorless solid, mp 65−70 °C, 74% (0.28 g), $[\alpha]_D$: +30.0 (c 0.1, $CHCl_3$), IR (neat cm^{-1}): 1450, 1302, 1110, 850, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.80 (d, $J = 8.4$ Hz, 1H, Ar), 7.61 (s, 1H, Ar), 7.52 (dd, $J =$ 1.2 and 8.4 Hz, 1H, Ar), 5.12 (d, $J = 5.2$ Hz, 1H, H-10b), 3.89 (dd, $J = 5.2$ and 14.4 Hz, 1H, H-5a), 3.76–3.51 (m, 6 H, H-4, –$\underline{C}H_2OCH_3$, and –OCH_3), 3.49–3.30 (m, 8H, H-2, H-5b, and 2 × –OCH_3), 3.20 (t, $J = 8.4$ Hz, 1H, H-3), 2.78–2.60 (m, 1H, H-4a), 1.30 (s, 9H, –SArC($C\underline{H}_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.7, 136.5, 133.4, 126.6, 124.6, 123.5 (Ar), 81.2 (C-3), 78.4 (C-4), 73.6 (C-2), 70.9 (–$\underline{C}H_2OCH_3$), 70.4 (C-10b), 60.2 (–OCH_3), 59.9 (–OCH_3), 59.2 (–OCH_3), 49.5 (C-5), 40.1 (C-4a), 35.2 (–SAr$\underline{C}$(CH_3)$_3$), 31.0 (–SArC($\underline{C}H_3$)$_3$). HRMS (ESI): *m/z* [M + H^+] calcd for $C_{20}H_{30}NaO_6S$ 399.18.41; found: 399.1837.

3,4–6-Tri-*O*-Benzyl-D-galactal (**26**) (Madhusudan et al. 2005): *Tri-O*-acetyl-galactal **25** (10.0 g, 36.7 mmol) was dissolved in 20 mL THF and finely crushed NaOH (17.0 g, 0.425 mol) was added. The reaction mixture was left for 3 h at room temperature. *Tetra-n*-butylammonium iodide (TBAI) (2.0 g, 6.0 µmol) and benzylbromide (15 mL, 0.13 mol) were added to the reaction and the reaction mixture was left to stir for 12 h. TLC analysis indicated the completion of the reaction, which was then quenched with water and the organic layer was extracted with ethyl acetate, washed with water and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure and a light yellow oil appeared. This was purified by column chromatography on silica gel using hexane and ethyl acetate. (5:1) as eluent to provide the title compound **26**: yellow oil, 64% (9.97 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24–7.15 (m, 15H, Ar), 6.26 (dd, $J = 1.2$ and 6.4 Hz, 1H, H-1), 4.82–4.74 (m, 2H, H-2, and –OC$\underline{H}_A$H$_B$Ph), 4.57–4.50 (m, 3H, 3 × –OCH$_A$$\underline{H}_B$Ph), 4.39 (d, $J = 12.0$ Hz, 1H, –OC$\underline{H}_A$H$_B$Ph), 4.31 (d, $J = 11.6$ Hz, 1H, –OC$\underline{H}_A$H$_B$Ph), 4.10–4.02 (m, 2H, H-4, and H-5), 3.85–3.83 (m, 1H, H-3), 3.67 (dd, $J = 7.4$ and 10.2 Hz, 1H, H-6a), 3.53 (dd, $J = 5.2$ and 10.0 Hz, 1H, H-6b); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 128.5, 128.4, 128.3, 128.0, 127.3, 127.2, 126.8, 126.7, 126.6 (Ar), 77.9 (C-3), 74.5 (C-4), 73.6 (–O$\underline{C}H_2$Ph), 72.1 (–O$\underline{C}H_2$Ph), 71.5 (–O$\underline{C}H_2$Ph), 71.0 (C-6), 69.1 (C-5), 61.5 (C-1), 58.4 (C-2). The spectroscopic data were in agreement with the literature report (Fischer and Hamann 1995).

3,4,6-Tri-*O*-benzyl-1,5-anhydro-2-deoxy-1,2-*C*-(dichloromethylene)-D-*glycero*-D-*galacto*-hexitol (**27**) (see preparation of **19** for protocol): colorless oil, 56% (5.3 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.24 (m, 15 H, Ar), 4.94–4.38 (m, 7 H, H-1, and 3 × –OC$\underline{H}_2$Ph), 3.88–3.87 (m, 2H, H-6a, and H-6b), 3.61–3.51 (m, 3H, H-3, H-4, and H-5), 1.97–1.94 (m, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$ MHz) δ: 138.7, 138.0, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6 (Ar), 77.8 (C-3), 75.1 (C-7), 74.4 (C-4), 73.4 (–O$\underline{C}H_2$Ph), 72.1 (–O$\underline{C}H_2$Ph), 71.4 (–O$\underline{C}H_2$Ph), 71.0 (C-6), 69.0 (C-5), 61.6 (C-1), 58.5 (C-2). The spectroscopic data were in agreement with the literature report (Ramana et al. 1997).

3,4,6-Tri-*O*-benzyl-1,5-anhydro-2-deoxy-1,2-*C*-methylene-D-*glycero*-D-*galacto*-hexitol (**28**) (see preparation of **20** for protocol): colorless oil, 52% (2.24 g); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.28 (m, 15H, Ar), 4.85–4.48 (m, 6H, 3 × –OC$\underline{H}_2$Ph), 3.81–3.59 (m, 6H, H-1, H-3, H-4, H-5, H-6a, and H-6b), 1.21–1.18 (m, 1H, H-2), 0.78–0.74 (m, 1H, H-7a), 0.45–0.38 (m, 1H, H-7b); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.8, 138.4, 138.3, 128.4, 128.3, 127.5, 127.4 (Ar), 74.8 (C-3), 73.5 (C-4), 73.3 (C-5), 73.2 (–O$\underline{C}H_2$Ph), 71.2 (–O$\underline{C}H_2$Ph), 69.2 (–O$\underline{C}H_2$Ph), 48.8 (C-6), 14.3 (C-1), 11.3 (C-7). The spectroscopic data were in agreement with the literature report (Ramana et al. 1997).

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-iodomethyl-α and β-D-galactopyranoses (**29**) (see preparation of **21** for protocol): golden oil, 62% (1.75 g), IR (neat cm^{-1}): 1771, 1495, 1453, 1223, 1086, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ: α-anomer 7.38–7.10 (m, 15H, Ar), 6.32 (d, $J = 3.2$ Hz, 1H, H-1), 4.86–4.38 (m, 6H, 3 × –OC$\underline{H}_2$Ph), 4.05–3.83 (m, 2H, H-4, and H-5), 3.74–3.44 (m, 4H, H-3, H-6a, H-6b, and H-7a), 2.95–2.87 (m, 1H, H-7b), 2.77–2.66 (m, 1H, H-2), 2.08 (s, 3H, OAc); δ: β-anomer δ: 5.55 (d, $J = 8.8$ Hz, 1H, H-1), 3.29 (dd, $J = 2$ and 10 Hz, 1H, H-7b), 2.10 (s, 3H, OAc), 1.93–1.83 (m, 1H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ: α-anomer 169.90 (C=O), 138.4, 137.7, 137.5, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7 (Ar), 94.1 (C-1), 78.8 (C-3), 74.5 (–OCH_2Ph), 74.1 (C-4), 73.7 (–OCH_2Ph), 72.3 (–OCH_2Ph), 71.5 (C-5), 68.3 (C-6), 40.7 (C-2), 20.9 (OAc), 2.7 (C-7); δ: β-anomer δ: 168.9 (C=O), 138.4, 137.8, 137.5, 128.6, 128.3, 128.1, 128.0, 127.8, 127.7 (Ar), 95.2 (C-1), 80.1 (C-3), 74.5, 73.5 (–OCH_2Ph), 72.0 (C-4), 71.0 (C-5), 68.0 (C-6), 39.6 (C-2), 21.0 (OAc), 5.7 (C-2). HRMS (ESI): *m/z* [M + Na]$^+$ calcd 677.2913; found 677.2899.

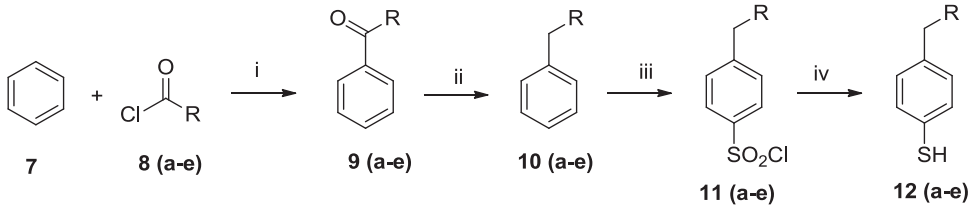
1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(4-*tert*-butylphenyl)thiomethyl -α and β-D-galactopyranoses (**30**) (see preparation of **22** for protocol): colorless syrup, 70% (0.9 g), IR (neat cm^{-1}): 1770, 1498, 1454, 1130, 698; ^1H NMR (400 MHz, $CDCl_3$) δ: β-anomer 7.40–7.10 (m, 19H, Ar), 5.65 (d, $J = 9.2$ Hz, 1H, H-1), 4.82 (d, $J = 11.6$ Hz, 1H, –OC$\underline{H}_A$H$_B$Ph), 4.61–4.20 (m, 5H, the remaining –OC$\underline{H}_2$Ph), 4.05–3.86 (m, 2H, H-4, and H-5), 3.78–3.45 (m, 3H, H-3, H-6a, and H-6b), 3.38 (dd, $J = 3.6$ and 13.6 Hz, 1H, H-7a), 3.15 (dd, $J = 3.2$ and 13.6 Hz, 1H, H-7b), 2.70–2.62 (m, 1H, H-2), 1.92 (s, 3H, OAc), 1.23 (s, 9H, –SArC(C$\underline{H}_3$)$_3$); δ: α-anomer 6.36 (d, $J = 3.2$ Hz, 1H, H-1), 2.82–2.70 (m, 1H, H-2), 2.57 (dd, $J = 11.2$ and 13.2 Hz, 1H, H-7b), 1.98 (s, 3H, OAc), 1.26 (s, 9H, –SArC(C$\underline{H}_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: β-anomer 168.8 (C=O), 149.6, 138.5, 137.7, 133.4, 130.1, 128.5, 128.4, 128.2, 128.1, 128.0, 127.8, 127.7, 127.5, 126.0 (Ar), 92.6 (C-1), 77.9 (C-3), 74.6 (C-4), 74.4 (–O$\underline{C}$H$_2$Ph), 74.2 (–O$\underline{C}$H$_2$Ph), 74.0 (–O$\underline{C}$H$_2$Ph), 71.3 (C-5), 68.5 (C-6), 38.9 (C-2), 34.4 (–SAr$\underline{C}$(CH$_3$)$_3$), 31.6 (C-7), 31.3 (–SArC($\underline{C}$H$_3$)$_3$), 20.9 (OAc); δ: α-anomer 169.1 (C=0), 149.1, 138.5, 138.8, 132.7, 129.0, 128.4, 128.2, 128.0, 127.9, 127.8, 127.6, 126.0 (Ar), 93.4 (C-1), 78.5 (C-3), 74.0 (–O$\underline{C}$H$_2$Ph), 73.5 (–O$\underline{C}$H$_2$Ph), 71.6 (C-4), 71.5 (–O$\underline{C}$H$_2$Ph), 70.4 (C-5), 68.1 (C-6), 41.2 (C-2), 34.4 (–SAr$\underline{C}$(CH$_3$)$_3$), 31.3 (C-7), 31.2 (–SArC($\underline{C}$H$_3$)$_3$), 21.0 (OAc). HRMS (ESI): *m/z* $[M + Na]^+$ calcd 677.2913; found 677.2899.

(2*R*,3*R*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-[(benzyloxy) methyl]-9-(*tert*-butyl)-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (**31**) (see preparation of **23** for protocol): white solid, mp 145–150 °C, 68% (505 mg), $[\alpha]_D$: +45.5 (c 0.1, $CHCl_3$), IR (neat cm^{-1}): 1478, 1134, 1103, 697; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.62 (d, $J = 1.2$ Hz, 1H, Ar), 7.37–7.09 (m, 16H, Ar), 6.98 (d, $J = 8.4$ Hz, 1H, Ar), 5.14 (d, $J = 5.6$ Hz, 1H, H-10b), 4.90 (d, $J = 11.6$ Hz, 1H, –OC$\underline{H}_A$H$_B$Ph), 4.74 (d, $J = 11.2$ Hz, 1H, –OC$\underline{H}_A$H$_B$Ph), 4.61–4.50 (m, 2H, 2 × –OCH$_A$$\underline{H}_B$Ph), 4.49 (d, $J = 12.0$ Hz, 1H, –OC$\underline{H}_A$H$_B$Ph), 4.42 (d, $J = 12.0$ Hz, 1H, –OCH$_A$$\underline{H}_B$Ph), 3.92–3.88 (m, 2H, –C$\underline{H}_2$OBn), 3.61–3.58 (m, 3H, H-2, H-3, and H-4), 3.29–3.25 (m, 2H, H-5a, and H-5b), 3.08–2.99 (m, 1H, H-4a), 1.22 (s, 9H, –SArC(C$\underline{H}_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.9, 138.3, 131.0, 128.4, 128.2, 127.8, 127.6, 125.9, 124.7 (Ar), 74.4 (C-4), 73.4 (–O$\underline{C}$H$_2$Ph), 72.9 (2 × –O$\underline{C}$H$_2$Ph), 72.7 (C-2 and C-5), 72.4 (C-10b), 71.8 (–$\underline{C}$H$_2$OBn), 34.4 (C-5), 33.1 (–SAr$\underline{C}$(CH$_3$)$_3$), 31.2 (–SArC($\underline{C}$H$_3$)$_3$), 26.8 (C-4a). HRMS (ESI): *m/z* $[M + H]^+$ calcd: 595.2877; found: 595.2880.

2*R*,3*R*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-[(benzyloxy) methyl]-9-(*tert*-butyl)-,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran *S,S*-dioxide (**32**) (see preparation of 24 for protocol): white solid, mp 155–160 °C, 72% (303 mg), $[\alpha]_D$: +55.0 (c 0.1, $CHCl_3$), IR (neat cm^{-1}) 1455, 1299, 1105, 749, 695; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.77 (d, $J = 6.9$ Hz, 1H, Ar), 7.65 (s, 1H, Ar), 7.45 (dd, $J =$ 1.2 and 8.4 Hz, 1H, Ar), 7.37–7.19 (m, 15 H, Ar), 5.18 (d, $J = 5.2$ Hz, 1H, H-10b), 4.82 (d, $J = 11.4$ Hz, 1H, –OC$\underline{H}_A$H$_B$Ph), 4.62 (d, $J = 10.2$ Hz, 1H, –OC$\underline{H}_A$H$_B$Ph), 4.58 (d, $J = 10.2$ Hz, 1H, –OCH$_A$$\underline{H}_B$Ph), 4.50–4.40 (m, 2H, –OC$\underline{H}_A$$\underline{H}_B$Ph), 4.38 (d, $J = 11.4$ Hz, 1H, –OCH$_A$$\underline{H}_B$Ph), 3.98 (dd, $J = 2.0$ and 11.2 Hz, 1H, H-4), 3.90 (dd, $J = 4.4$ and 14.4 Hz, 1H, H-5a), 3.84–3.78 (m, 1H, H-3), 3.67–3.50 (m, 2H, H-2 and –C$\underline{H}_A$H$_B$OBn), 3.42–3.20 (m, 3H, H-4a, H-5b, and –CH$_A$$\underline{H}_B$OBn), 1.18 (s, 9H, –SArC(C$\underline{H}_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.8, 138.2, 137.9, 133.5, 128.6, 128.0, 127.9, 127.8, 124.7, 126.34 (Ar), 76.2 (C-4), 74.4 (–O$\underline{C}$H$_2$Ph), 73.6 (C-2), 73.0 (C-3), 72.1 (2 × –O$\underline{C}$H$_2$Ph), 71.9 (C-10b) 70.0 (C-10a), 49.8 (C-5), 36.0 (–SAr$\underline{C}$(CH$_3$)$_3$), 35.3 (C-4a), 30.9 (–SArC($\underline{C}$H$_3$)$_3$). HRMS (ESI) *m/z* $[M + Na]^+$ calcd: 644.3040; found: 644.3038.

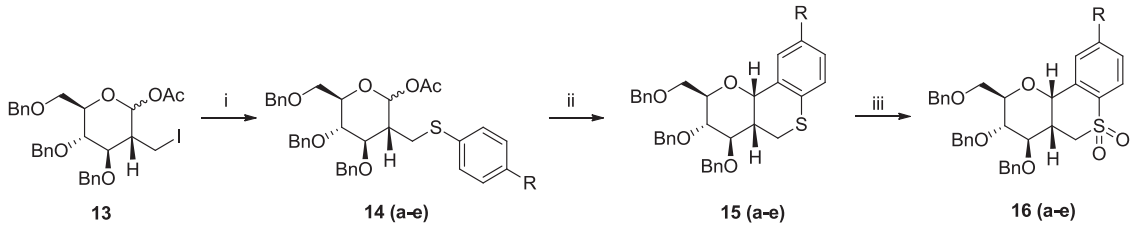
In vitro antimalarial assay

The in vitro antimalarial activity of test samples against the 3D7 strains of the malaria parasite, *P. falciparum*, is measured by parasite survival using parasite lactate dehydrogenase (pLDH) assay (Makler et al. 1993). This enzymatic assay involves the parasite lactate dehydrogenase, which is distinguishable from the host lactate dehydrogenase. Lactate dehydrogenase is an enzyme found in all cells and catalyzes the formation of pyruvate from lactate reducing a coenzyme NAD (nicotinamide adenine dinucleotide) to NADH. In parasites, the NAD analog APAD (3-acetylpyridine adenine nucleotide) is reduced to APADH and upon this reduction the yellow NBT/PES (nitro blue tetrazolium + phenazine ethosulphate) is converted to purple formazan crystals. The absorbance is read at 620 nm using a multiwell spectrophotometer (Infinite F500). The formation of these crystals indicates the pLDH activity and therefore the survival of parasites. The percentage survival of parasites is a measure of a compound's inhibitory activity against *P. falciparum*. This inhibitory activity is determined by the IC_{50} (50% Inhibitory Concentration) and is measured by making 10 three-fold serial dilutions of the test samples in triplicate in a transparent 96-well flat bottom plate (Netstar). The plate is put in an air-tight box, gassed and incubated for 48 h followed by developing with NBT/PES reagent. The IC_{50} values are expressed as the percentage parasite survival relative to the control, calculated from fitted sigmoidal dose–response curves. The dose–response curves were obtained by plotting percentage parasite survival against the logarithm of the concentration using the GraphPad Prism software package (GraphPad software, Inc, California, USA). IC_{50} values were calculated graphically by extrapolation from these curves. The Z'-factor for all the tests was found to be between 0.5 and 1.0. (See supporting information for data and graphs). Compound inhibitory activity is determined by



a: R = ethyl; **b:** R = *sec*-butyl; **c:** R = *n*-pentyl; **d:** R = *n*-heptyl; **e:** R = *n*-heptadecyl

Scheme 1 (i) $AlCl_3$, CH_2Cl_2, 40 °C, 4 h, (68–78%); (ii) Zn, HCl, H_2O, 100 °C, 6 h, (56–80%); (iii) HSO_3Cl, CH_2Cl_2, rt, 6 h, (53–77%); (iv) $LiAlH_4$, Et_2O, 35 °C, 24 h, (71–83%)



a: R = propyl; **b:** R = 2-methylbutyl; **c:** R = *n*-hexyl; **d:** R = *n*-octyl; **e:** R = *n*-octadecyl

Scheme 2 (i) NaH, Aryl thiol, DMF, rt, 10 min, (83–94%); (ii) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 15 min, (68–81%); (iii) OXONE® (2 equiv), Al_2O_3, CH_2Cl_2, rt, 12 h, (63–78%). **a** R=propyl; **b** R=2-methybutyl; **c** R=n-hexyl; **d** R=n-octyl; **e** R=n-octadecyl

preparing test samples in parasite culture medium in transparent 96-well flat bottom plates (Greiner Bio-one)—100 µM starting concentration in three-fold serial dilutions, to obtain 11 decreasing concentrations ($n = 4$ for each data point). Parasitized red blood cells are added to a final concentration of 1% hematocrit, 2% parasitaemia and the plates incubated for 48 h before proceeding with the pLDH assay. Percentage parasite survival in each well is calculated relative to control wells that receive no drug. Results are presented as percentage parasite viability at the various compound concentrations, with the IC_{50} values of individual compounds calculated from fitted sigmoidal dose-response curves. In accordance to our previous report (Kinfe et al. 2014), test compounds that show parasite survival of $< 15\%$ at a single concentration of 10 µM are screened further for dose-response to determine their IC_{50} values. From the dose-response curves, compounds that exhibit ≤10 µM IC_{50} values are considered active while those with > 10 µM are considered inactive. Compounds with IC_{50} values of < 3 µM are considered highly active.

Results and discussion

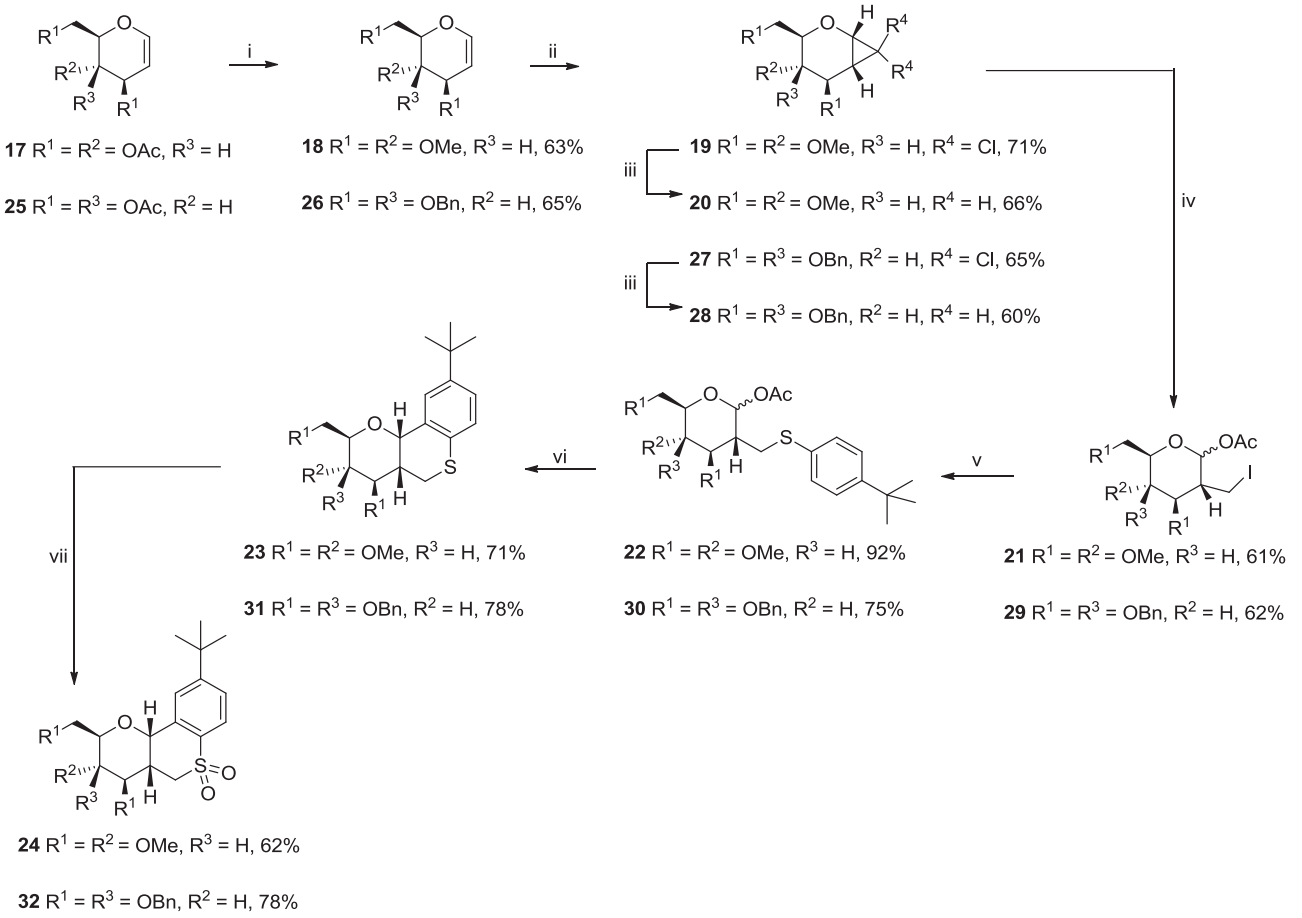
Synthesis of carbohydrate-derived thiochromans possessing aliphatic substituents on the thiophenol moiety

Encouraged by the impressive antimalarial properties of the sulfone thiochroman **1** (Kinfe et al. 2014), we successfully synthesized thiochroman derivatives **16a**−**e** with increased lipophilicity, in order to investigate if this would improve antimalarial activity. Since the sulfone and sulfoxide derivatives exhibited similar activity (Kinfe et al. 2014), we decided to investigate the sulfone analogs only in the current study. To achieve our aims, commercially scarce thiols possessing aliphatic groups were prepared according to Scheme 1. Friedel-Crafts acylation of benzene, followed by Clemmensen reduction to afford alkyl substituted benzene derivatives **10a**−**e** in reasonable yields. Sulfonation of these derivatives using chlorosulfonic acid in DCM provided products **11a**−**e**. $LiAlH_4$ reduction in anhydrous diethyl ether then gave the thiol derivatives **12a**−**e**, ready to be used in thiochroman synthesis.

The *para*-alkyl substituted aryl thiols were converted into their thiolate derivatives and treated with iodomethyl glycosyl **13**, prepared from glucal according to our previously reported protocol, to form sulfides **14a**−**e** as illustraited in Scheme 2 (Kinfe et al. 2014). These were then cyclised to form thiochromans **15a**−**e**, which upon oxidation with OXONE® led to the formation of the target sulfone derivatives **16a**−**e**.

Synthesis of methyl-protected carbohydrate-derived thiochroman analogs

In our previous study, it was established that replacing the benzyl-protecting group of the sugar moiety with an "acyl" or "H" led to diminished antimalarial activity (Fig. 1) (Kinfe et al. 2014). Thus it was imperative to prepare the methyl-



Scheme 3 Reaction conditions: (i) NaOH, TBAI, MeI, THF, rt, 16 h; (ii) NaOH (50% aq), TBACl, $CHCl_3$, 35 °C, 8 h; (iii) $LiAlH_4$, THF, rt, 36 h; (iv) NH_4I, Ac_2O, H_2O_2, CH_3CN:AcOH (1:1), 0 °C to rt, 1 h; (v) NaH, 4-*tert*-butylthiophenol, DMF, rt, 10 min; (vi) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 15 min; (vii) OXONE® (2 equiv), Al_2O_3, CH_2Cl_2, rt, 12 h

protected analog **24** to investigate whether the activity is due to the mere presence of the "benzyl" or the "ether" functional group. The synthesis of the methyl analog **24** was accomplished by adopting the methodology developed for the benzyl-protected derivative **1** as depicted in Scheme 3. The synthesis commenced with the exchange of the acetate protecting group of the commercially available glycal **17** with a methyl group in order to provide glycal **18**. Cyclopropanation of the double bond of glycal **18** using an in situ generated dichlorocarbene followed by $LiAlH_4$ reduction afforded the cyclopropanated sugar derivative **20**. Treatment of the cyclopropanated sugar **20** with NH_4I and H_2O_2 in a mixture of AcOH:Ac_2O:CH_3CN furnished glycosyl acetate **21** via a regioselective ring opening of the cyclopropyl moiety. Substitution of the iodine atom in **21** with *para-tert*-butylthiophenolate followed by a stereoselective intramolecular Friedel-Crafts alkylation and subsequent oxidation provided the desired sulfone derivative **24** (Scheme 3).

Synthesis of the galactal analog of the carbohydrate-derived thiochromans

On the basis of our group's previous study that demonstrated that the antimalarial activity of the thiochromans was dependent on the orientations of the C-2 (*gluco* vs. *manno*) and C-1 (α vs. β) substituents of the sugar moiety (Kinfe et al. 2014), we also synthesized a galactal analog of **1** in order to investigate the effect of the C-4 stereochemistry. To achieve this, acetylated galactal **25** that already has an axial substituent at C-4 was used as the preferred starting material. This was transformed through a series of reaction steps into its thiochroman analog according to Scheme 3. These reaction steps and reaction conditions are similar to those reported for the synthesis of sulfone **24**, starting with the benzylation of galactal **25** to afford its benzylated derivative **26**. Dihalocyclopropanation, reduction and subsequent oxidative ring opening provided compound **29** containing a C-2 iodomethyl substituent. An S_N2 substitution on **29**

Table 1 In vitro antimalarial activities of the thiochroman derivatives **1**, **16a**–**e**, **24**, and **32** against chloroquine-sensitive (3D7) *P. falciparum* strains

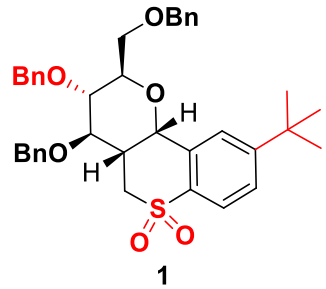
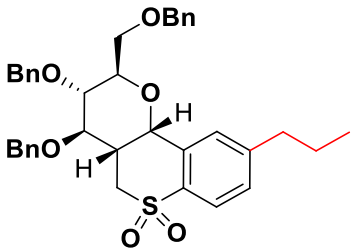
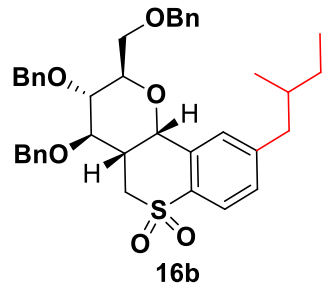
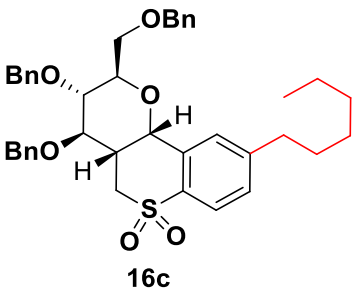
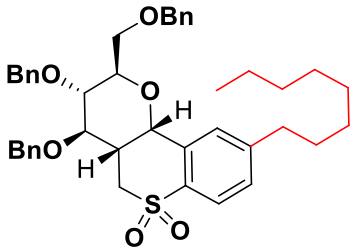
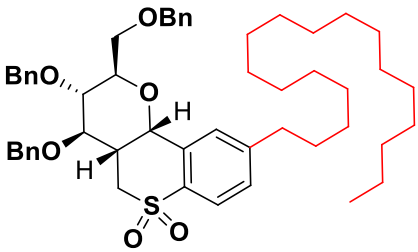
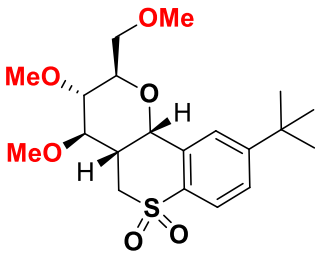
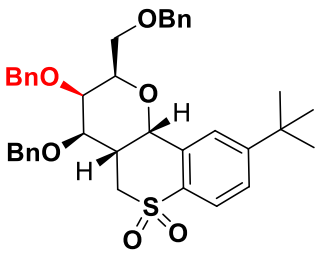
Entry	Thiochroman derivative	% Parasite survival ± SD @ 10 µM	% Parasite survival ± SD @ 1 µM	IC_{50} (µM)
1	 **1**	−5.10	25.26 ± 2.89	0.46
2	 **16a**	15.42 ± 3.02	23.49 ± 4.46	0.27
3	 **16b**	14.53 ± 0.70	47.88 ± 1.72	1.10
4	 **16c**	76.89 ± 2.32	95.65 ± 3.99	n/a[a]

Table 1 continued

Entry	Thiochroman derivative	% Parasite survival ± SD @ 10 µM	% Parasite survival ± SD @ 1 µM	IC_{50} (µM)
5	 **16d**	53.52 ± 2.03	65.35 ± 3.44	n/a[a]
6	 **16e**	20.50 ± 1.17	55.68 ± 3.99	n/a[a]
7	 **24**	34.49 ± 4.51	67.90 ± 2.35	n/a[a]
8	 **32**	35.75 ± 2.81	51.23 ± 2.18	n/a[a]
9	Chloroquine			0.01

[a] n/a not applicable. Since the compounds did not exhibit parasite survival of $< 15\%$ at a single concentration of 10 µM, they were not screened further for dose–response to determine their IC_{50} values

using *tert*-butyl thiophenolate afforded sulfide **30** in 75% yield. This was subsequently cyclized using BF_3•Et_2O to afford thiochroman **31** in 78% yield and further oxidized to its sulfone derivative **32** using excess OXONE®.

Antimalarial activity of carbohydrate-derived thiochromans 1, 16a−e, 24 and 32

Having successfully synthesized the target thiochromans **16a**−**e**, **24**, and **32** with lipophilic substituents, methyl-protected sugar moieties and the galactal analog, respectively, these compounds were then investigated for their in vitro antimalarial properties against 3D7 *P. falciparum* strains in parallel with thiochroman **1** and their activities are summarized in Table 1. Since the compounds previously tested showed almost similar activities against both strains of the *P. falciparum*, (Kinfe et al. 2014) the thiochroman derivatives in the current study were evaluated for their activity against the 3D7 strain only. Thiochromans **1**, **16a**, and **16b** showed parasite survival of $< 15\%$ at a single concentration of 10 µM and were selected for further screening for dose–response to determine their IC_{50} values. Thiochromans **16a** and **16b**, possessing *n*-propyl and 2-methylbutyl substituents, exhibited high antimalarial activities with IC_{50} values of 0.27 and 1.10 µM, respectively. The activity of thiochroman **16a** was almost similar to the activity of the thiochroman analog **1** (IC_{50} value of 0.46 µM). With an almost three-fold lower IC_{50} value, thiochroman **16a** was more potent than **16b**. Lengthening the alkyl chains beyond four-linear carbons proved unfavorable as this diminished the activities of these compounds, as evidenced by compounds **16c–e**. Disappointingly, in vitro antimalarial evaluation of the methyl-protected sulfone **24** demonstrated less activity at 1 and 10 µM concentrations ($> 15\%$ parasite survival) compared to the corresponding benzyl-protected analog **1**. This confirmed that the presence of the "benzyl" group was indeed crucial for the activity of the thiochroman scaffolds. Similarly, the galactal analog **32** exhibited poor activity at 1 and 10 µM concentrations ($> 15\%$ parasite survival), reaffirming the dependence of the antimalarial activity of the thiochromans on the orientation of the substituents on the carbohydrate moiety, and that in this case the preference of C4-OR is for an equatorial position.

In conclusion, these results indicate that carbohydrate-based thiochromans with bulky lipophilic aromatic substituents such as *tert*-butyl groups and branched short chains, rather than long linear alkyl chains, possess promising antimalarial activity. Furthermore, in addition to the sulfur's oxidation state and the presence of short lipophilic substituents, the antimalarial property of these compounds is dependent on the presence of "benzyl" protecting group on the sugar moiety. Moreover, the glucosyl (equatorial orientation of the C-4 substituent on the sugar moiety), as opposed to the galactosyl (axial C-4 orientation of substituents), is vital for the high activity of the thiochromans and this is in agreement with the previous report (Kinfe et al. 2014) where it was shown that the glucosyl sugar moiety was more potent than the mannosyl analog. Having established the structural features that are important for the antimalarial activity of the thiochromans, we are currently synthesizing sulfoximine analogs of the active thiochromans in the hope of obtaining better activity (IC_{50} values of lower nano-molar concentrations).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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