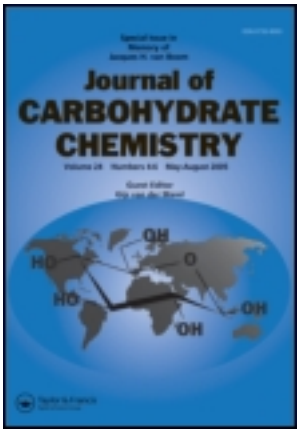

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Facile Diastereoselective Synthesis of Carbohydrate-Based Thiochromans

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Facile Diastereoselective Synthesis of Carbohydrate-Based Thiochromans

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An efficient and novel diastereoselective thiochroman synthesis using the carbohydrate chiral pool via intramolecular Friedel-Crafts alkylation is presented. The scope and limitations of the method are investigated.

Keywords Thiochroman; Carbohydrate; Friedel-Crafts Alkylation

INTRODUCTION

3,4-Dihydro-2*H*-1-benzothiopyranas, commonly known as thiochromans, are privileged fused rings that have received special attention due to their presence as substructures in many interesting biologically active compounds, such as those used in the treatment of depression, schizophrenia, Alzheimer's disease, and Parkinson's disease, as well as those with anticancer activity.[1–3]

Due to their important role in medicinal chemistry, these types of compounds have attracted significant interest from synthetic organic chemists, resulting in the development of a number of synthetic methodologies for the synthesis of such compounds. The two strategies commonly employed for the synthesis of thiochromans are (1) the thio-Claisen rearrangement of ally phenyl sulfides[4,5] and (2) acid-catalyzed intermolecular cycloaddition of α,β-unsaturated aldehydes with arylthiols.[2,6–10] Stereoselective thiochroman synthesis can be achieved either via stereoselective derivitazation of a thiochroman[11–13] or through stereoselective cycloaddition reactions.[3,14–17] Although

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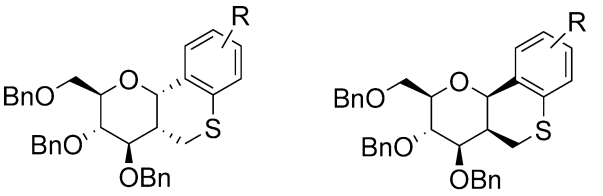
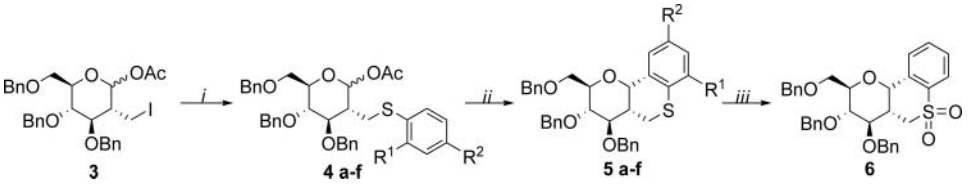


Figure 1: General structure of proposed carbohydrate-based thiochromans.

these strategies are efficient in terms of selectivity, the need for special catalysts that are not readily or commercially available calls for the development of new alternative strategies. These alternatives should be highly stereoselective and utilize cheap and readily available substrates and/or catalysts to supplement the existing methodologies. A possible strategy of the aforementioned alternatives would involve the use of readily available chiral building blocks such as carbohydrates, which are abundant renewable chiral building blocks and employed extensively in the synthesis of valuable organic molecules.[18] However, to the best of our knowledge, their use in the stereoselective synthesis of thiochromans has not been explored and herein we report the first example for diastereoselective synthesis of carbohydrate-based thiochromans whose general structures are depicted in Figure 1.

In this context, we envisioned that the tricyclic unit of the thiochromans in the general structures (Fig. 1) might be assembled starting from the glycosyl iodoacetate, readily constructed using the protocol reported by Gammon and coworkers for ring opening of cyclopropanated sugars,[19] followed by substitution of the iodide with a suitably substituted arylthiolate and intramolecular Friedel-Crafts alkylation at the anomeric center as shown in Scheme 1. It was expected that a glycosyl starting material would afford thiochroman **1** while a mannosyl substrate would result in the formation of thiochroman **2**.



Scheme 1: *i*) NaH, ArSH, DMF, rt, 5 min (see Table 1 for yields); *ii*) $BF_3{\cdot}Et_2O$, DCM, 0°C, 5 min (see Table 1 for yields); *iii*) oxone, wet alumina, DCM, rt, overnight, 78%.

RESULT AND DISCUSSION

In achieving our goals, we started with glycosyl iodoacetate **3** synthesized from α-1,2-cyclopropanated sugar[19] and thiophenol to establish optimum reaction

conditions for the synthesis of the target thiochromans. Thus, sulfide **4a** ($R^1 = R^2 = H$) was prepared in 83% yield by reaction of glycosyl iodoacetate **3** with freshly prepared sodium thiophenolate in DMF at rt for 5 min (Sch. 1). It is important to mention that prolonged reaction time of more than 10 min resulted in formation of several by-products, lowering the yield of the desired product. Treatment of sulfide **4a** with $BF_3{\cdot}Et_2O$ in dry DCM in the presence of molecular sieves at 0°C for 5 min afforded thiochroman **5a** in 69% yield as a white solid having the glucose configuration (Sch. 1).

The structure of thiochroman **5a** was established using ^1H, ^{13}C, and NOESY NMR spectroscopies. The decrease in the integration of the aromatic protons from 20 in iodoacetate **4a** to 19 in thiochroman **5a,** coupled with the upfield shift of the anomeric proton to δ_H 5.13 and the disappearance of the acetate group signal in the absence of any external nucleophile during the cyclization reaction, reasonably indicates intramolecular alkylation at C-1. This was supported by ^{13}C NMR spectroscopy, which displayed an upfield shift of C-1. The anomeric configuration was determined by measuring the $^3J_{H\text{-}1,H\text{-}2}$ coupling constant. The $^3J_{H\text{-}1,H\text{-}2}$ coupling constant was found to be 5.6 Hz for thiochroman **5a** and corresponds to a *gauche* relationship between the H-1 and H-2 protons. Since the stereochemistry at C-2 is fixed, a *gauche* relationship between H-1 and H-2 is possible if the H-1 proton is equatorially oriented and, thus, confirms that the anomeric configuration of thiochroman **5a** is α-anomer.[20] Attempts to grow crystals of thiochroman **5a** for absolute structure determination using X-ray crystallography were unsuccessful. However, oxidation of thiochroman **5a** using excess oxone in the presence of wet alumina[21] resulted in formation of sulfone **6** in 78% yield as white crystals. As only one pure isomer is present from the synthesis, the compound crystallizes in the noncentrosymmetric $P2_12_12_1$ space group, with the Flack parameter indicating the correct isomer refined (Fig. 2). Ring puckering analysis[22] for the pyranosyl ring gave $q_2 = 0.033(7)$ Å, $q_3 = -0.584(6)$ Å, $Q = 0.585(6)$ Å, $\theta = 177.1(7)°$, and $\varphi = 263(11)°$, proving that it is a chair conformation, whereas the puckering analysis for the thiochroman ring gave $q_2 = 0.365(7)$ Å, $q_3 = 0.332(6)$ Å, $Q = 0.585(6)$ Å, $\theta = 47.8(8)°$, and $\varphi = 251.4(9)°$, proving an envelope conformation. The crystal structure is stabilized by several C-H . . . O and CH . . . π interactions.[23]

To investigate the generality and scope of the synthetic methodology, several *ortho* and *para* substituted arylthiols were tested. These provided the corresponding thiochromans in good to excellent yields. The results are summarized in Table 1 (entries 1–6) with the products identified by ^1H and ^{13}C NMR spectroscopy. Unfortunately, the cyclization resulted in a difficult-to-separate mixture of products when *para* halide or *meta* substituted arylthiols were used. A possible explanation for this could be due to the *ortho-meta* and *ortho-para* directing competitions between the sulfur and the respective aryl substituents, resulting in competitive Friedel-Crafts alkylations.

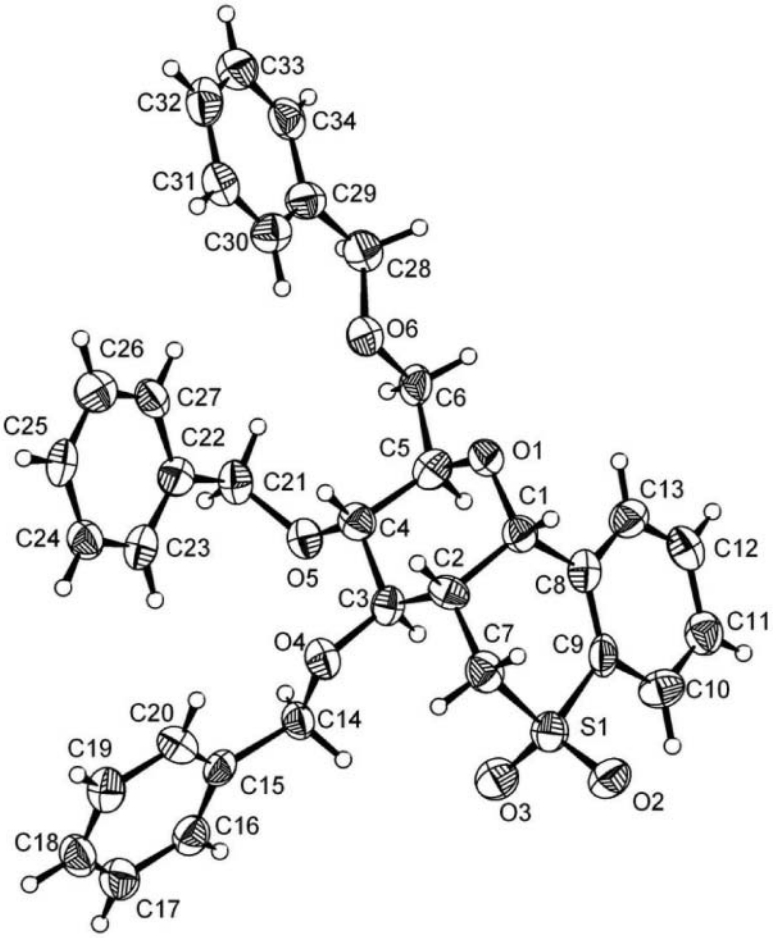
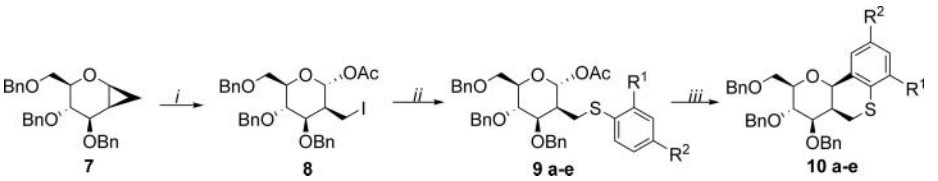


Figure 2: Single X-ray crystal structure of sulfone **6**, showing atom labeling and thermal ellipsoids drawn at 50% probability.

Under similar reaction conditions and sequences, thiochromans **10a–e** (Table 1, entries 7–11), which have opposite stereochemistry at positions C-1 and C-2 to those of thiochromans **5a–f** (Table 1, entries 1–6), were obtained as pure isomers with mannosyl iodoacetate **8** as starting material (Sch. 2). The mannosyl iodoacetate **8** was prepared by opening of a β-1,2-cyclopropanated sugar **7** with NIS in the presence of water as a nucleophyl.[24] This was followed by acetylation of the anomeric hydroxyl group (Sch. 2). The structures of the products were established the same way as thiochroman **5a**. However, it was not possible to determine the anomeric configuration of thiochromans **10a–e** by simply measuring the $^{3}J_{\text{H-1,H-2}}$ coupling constant since in both possible anomers, the H-1 and H-2 protons possess the *gauche* relationship, which results in a small J value.[20] One way of proving the anomeric configuration is



Scheme 2: *i*) a. NIS, H_2O, THF, 50°C, 12 h; b. Ac_2O, DMAP, Et_3N, rt, 30 min, 93%; *ii*) NaH, ArSH, DMF, rt, 5 min (see Table 1 for yields); *iii*) $BF_3{\cdot}Et_2O$, DCM, 0°C, 5 min (see Table 1 for yields).

the size of the hetero-coupling constant $^1J_{C\text{-}1,H\text{-}1}$ (>170 Hz for α-mannoside and <160 Hz for β-mannoside).[20] Unfortunately, the C-1 of thiochromans **10a–e** overlapped with the other carbon signals, making it difficult to measure the hetero-coupling constant $^1J_{C\text{-}1,H\text{-}1}$. Therefore, crystals of thiochroman **10a–e** were grown from different solvent systems and the absolute structures and anomeric configurations were determined using X-ray crystallography. The anomeric configuration was proved to be a β-mannoside for all thiochromans **10a–e**.

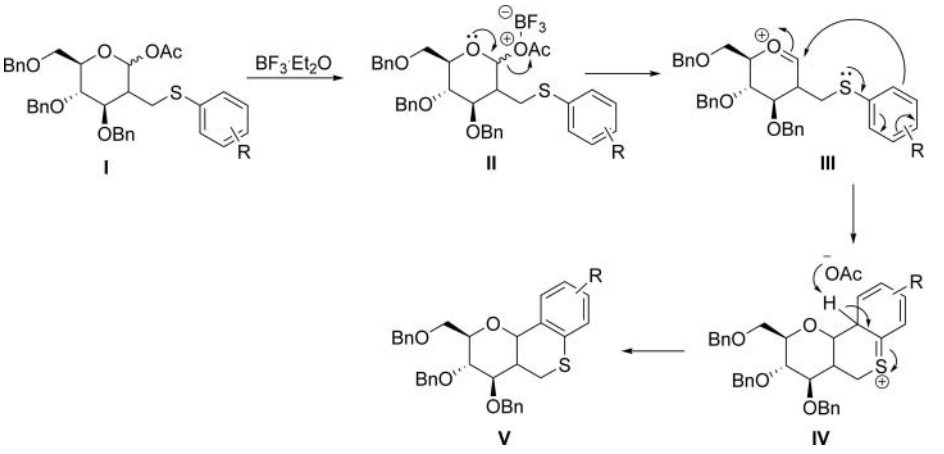
Concerning the proposed mechanism of the reaction, the formation of a single thiochroman isomer product suggests the formation of an oxocarbenium intermediate **III** formed via activation of the OAc leaving group by $BF_3{\cdot}Et_2O$. It is possible that the arylthiol moiety undergoes resonance[25] and attacks the electrophilic anomeric center intramolecularly to form a six-membered ring as shown in Scheme 3.

Selectivity in favor of the α-anomeric configuration for thiochromans **5a–f** could be explained in terms of the preference in the oxocarbenium intermediate for the $^4H_3$ conformation **VI** (Sch. 4).[26] In this conformation the thiophenyl

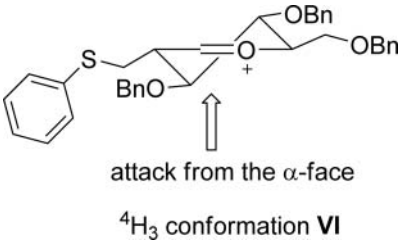
Table 1: Results of the arylthiolate substitution and thiochroman syntheses.

		Sulfides		Thiochromans	
Entry	Aromatic substituent	Product	% Yield	Product	% Yield
1	R^1=R^2= H	4a	83	5a	69
2	R^1= H, R^2= CH_3	4b	87	5b	71
3	R^1= CH_3, R^2= H	4c	87	5c	73
4	R^1= H, R^2= Bu^t	4d	93	5d	69
5	R^1= H, R^2= OCH_3	4e[a]	—	5e	70
6	naphtalene-2-thiol	4f	86	5f	68
7	R^1=R^2= H	9a	95	10a	75
8	R^1= H, R^2= CH_3	9b	80	10b	83
9	R^1= CH_3, R^2= H	9c	93	10c	94
10	R^1= H, R^2= Bu^t	9d	93	10d	70
11	R^1= H, R^2= OCH_3	9e	78	10e	92

[a]Sulfide **4e** was unstable on standing and thus it was immediately cyclized without purification.



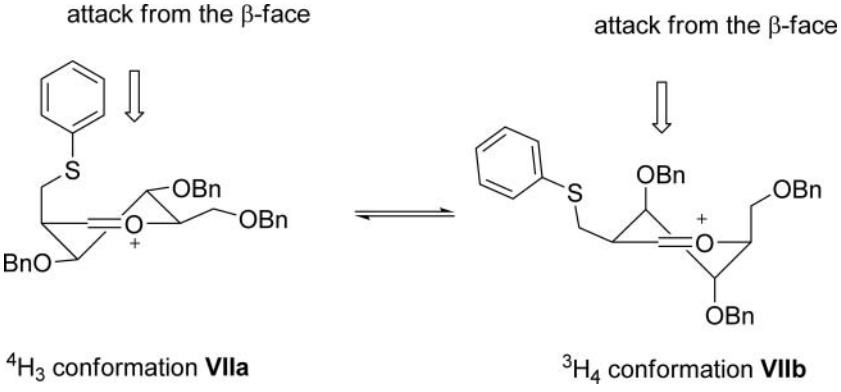
Scheme 3: Proposed mechanism for the formation of the carbohydrate-based thiochromans.



Scheme 4: Preferred conformation of oxocarbenium intermediate of a glucosyl pyranose.

moiety is prepositioned for intramolecular delivery from the α-face of the sugar.

In the case of the mannose analog, the selectivity for the β-anomer could be due to the intramolecular thiophenyl delivery to the β-face of the preferred $^3H_4$ oxocarbenium conformer **VIIb** (Sch. 5).[26,27] The formation of the β-anomer



Scheme 5: Possible conformations of oxocarbenium intermediate of a mannosyl pyranose.

thiochromans **10a–e** and the absence of formation of a twisted boat thiochroman as a result of nucleophilic attack at the β-face of the $^4H_3$ conformer **VIIa** suggests that the preferred conformation of the oxocarbenium intermediate in the mannose analogs is the $^3H_4$ conformer. This preference of the oxocarbenium conformation is in agreement with the literature reports.[26,27] The stability of the $^3H_4$ conformer is attributed to the stabilization of the positive charge by the C-3, C-4, and C-5 axially oriented alkoxy groups.[27a]

CONCLUSION

In conclusion, we have demonstrated an efficient synthetic protocol for diastereoselective preparation of novel carbohydrate-based thiochromans in which the orientation of the substituent at C-2 of the starting pyranosyl acetate induces the stereochemistry of the thiochroman products. 1α,2α-aryl-*C*-glycoside and 1β,2β−aryl-*C*-mannoside-type thiochromans (**1** and **2** in Fig. 1) were successfully synthesized as pure isomers from glycosyl and mannosyl iodoacetate substrates, respectively. To the best of our knowledge, this is the first report whereby a carbohydrate chiral pool is employed in diastereoselective synthesis of thiochromans. Besides the investigation of the synthesized thiochromans and their derivatives in medicinal chemistry, we are currently also investigating their use in the Corey-Chaykovsky reaction for asymmetric epoxidation and in the synthesis of the rather difficult *cis*-2-*C*-branched-aryl-*C*-glycosides and mannosides.

EXPERIMENTAL

All the solvents used were freshly distilled. Dichloromethane was distilled over phosphorous pentoxide in a condenser fitted with a drying tube containing calcium chloride. Other solvents were dried by appropriate techniques. All reagents were purchased from Sigma Aldrich. All reactions were monitored by thin layer chromatography (TLC) on aluminum-backed Merck silica gel 60 F_{254} 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 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 Thermovar hot-stage microscope and are uncorrected. Optical rotations were determined on a Perkin-Elmer 141 polarimeter in chloroform solutions at 25°C. The concentration *c* refers to g/100 mL. Infrared spectra were recorded using Tensor 27 Bruker and Perkin Elmer FT-IR spectrum BX.

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 nuclear magnetic resonance (^{13}C 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 spectrometers were recorded on a Walters API Quattro Micro spectrometer at the University of Stellenbosch, South Africa.

1,3,4,6-*Tetra*-*O*-acetyl-2-deoxy-2-*C*-iodomethyl-α and-β-D-gluco pyranoses (3)

This was synthesized according to the protocol reported by Gammon et al. and the spectroscopic data were in agreement with the literature reports.[19]

1,3,4,6-*Tetra*-*O*-acetyl-2-deoxy-2-*C*-iodomethyl-α-D-mannopyra nose (8)

To a solution of the β-1,2-cyclopropanated sugar **7** (2.55 mg, 5.92 mmol) in 30 mL of THF-H_2O (2:1), NIS (1.91 mg, 7.89 mmol) was added. The resulting mixture was stirred at 50°C for 12 h.[23] The residue was then taken up in ethyl acetate; washed successively with 10% $Na_2S_2O_3$, water, and brine; and dried over $MgSO_4$. The crude product was redissolved in DCM (20 mL) and treated with Et_3N (3 mL), a catalytic amount of DMAP, and Ac_2O (3 mL), and the resulting solution was then stirred at rt. After 30 min, the reaction mixture was diluted with DCM, washed successively with water and brine, and then dried over $MgSO_4$. The crude product was purified by column chromatography (ethyl acetate/petroleum ether, 5:95) to give the title compound in 93% yield as a colorless oil; $[\alpha]_D = +13.7$ (c 0.5, $CHCl_3$); IR (neat, cm^{-1}): 1752, 1496, 1453, 1226, 1096, 1026, 954, 735, 695.3; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.10 (m, 15H, aromatic), 6.32 (s, 1H, H-1), 4.78 (d, J = 10.8 Hz, 1 H, CH_AH$_B$Ph), 4.70–4.56 (m, 3H, C$H_A$$H_B$Ph), 4.53–4.40 (m, 2H, C$H_A$$H_B$Ph), 4.00–3.88 (m, 1H, H-3), 3.83–3.55 (m, 5H, H-5, H-4, H-6$_a$, H-6$_b$ and H-7$_a$), 3.11 (t, J = 10.8 Hz, 1H, H-7$_b$), 2.60–2.45 (m, 1H, H-2), 2.05 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.9 (OCOCH$_3$), 138.1, 137.9, 128.5, 128.4, 128.4, 128.0, 127.8, 127.7 (aromatic), 93.9 (C-1), 79.1 (C-3), 74.9 (CH$_2$Ph), 73.8 (C-4), 73.5 (CH$_2$Ph), 73.4 (C-5), 72.0 (CH$_2$Ph), 68.5 (C-6), 45.8 (C-2), 21.0 (OCOCH$_3$), 0.2 (C-7); HRMS (ESI): m/z [M+Na]$^+$ Calcd 639.1220; found: 639.1224.

General procedure for the substitution of the iodoacetates with arylthiols

To a solution of arylthiol (1.62 mmol) in DMF (20 mL), sodium hydride (60% dispersion on oil, 47 mg, 1.62 mmol) was added and the mixture was

vigorously stirred at rt for 5–10 min under nitrogen. A solution of iodoacetate **3** or **8** (900 mg, 1.35 mmol) in DMF (2 mL) was then added and after 5-min stirring of the reaction mixture, methanol (3 mL) was added dropwise and the resulting clear solution was concentrated in vacuo. The solution was directly submitted to silica gel chromatography (ethyl acetate/petroleum ether, 2:8) to give the corresponding sulfides:

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-phenylthiomethyl-D-glucopyranosyl (4a): 83% yield, 1:3 α:β anomeric mixture; colorless oil; IR ($CHCl_3$, cm^{-1}): 1752, 1483, 1452, 1137, 699; ^1H NMR ($CDCl_3$, 400 MHz) for β-anomer: δ 7.46–7.03 (m, 20H, aromatic), 5.66 (d, $J = 9.2$ Hz, 1H, H-1), 4.93 (d, $J = 10.8$ Hz, 1H, CH_AH$_B$Ph), 4.79 (d, $J = 10.4$ Hz, 1H, CH_AH$_B$Ph), 4.75–4.40 (m, 4H, the rest of the CH_2Ph), 3.90–3.70 (m, 5H, H-3, H-4, H-5, H-6$_a$ and H-6$_b$), 3.27 (dd, $J = 3.6$ and 13.2 Hz, 1H, H-7$_a$), 3.18 (d, $J = 13.2$ Hz, 1H, H-7$_b$), 2.32–2.18 (m, 1H, H-2), 1.98 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) for β-anomer: δ 168.9 (O*C*OCH$_3$), 138.1, 137.9, 137.8, 136.7, 129.8, 129.0, 128.4, 128.3, 127.9, 127.8, 127.7, 126.4 (aromatic), 93.1 (C-1), 80.3 (C-4), 79.0 (C-3), 75.4 (C-5), 74.9 (*C*H$_2$Ph), 73.6 (*C*H$_2$Ph), 73.5 (*C*H$_2$Ph), 73.0 (C-6), 46.1 (C-2), 31.4 (C-7), 20.9 (OCO*C*H$_3$); ^1H NMR ($CDCl_3$, 400 MHz) for α-anomer: δ 6.42 (s, 1H, H-1), 4.98 (d, $J = 11.2$ Hz, 1H, CH_AH$_B$Ph), 3.44 (d, $J = 13.2$ Hz, 1H, H-7$_a$), 2.57 (t, $J = 12.4$ Hz, 1H, H-7$_b$), 2.05 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) for α-anomer: δ 168.9 (O*C*OCH$_3$), 137.7, 135.6, 128.9, 128.5, 128.3, 128.0, 127.7, 127.6, 126.0 (aromatic), 92.0 (C-1), 80.2 (C-4), 78.8 (C-3), 75.3 (C-5), 74.9 (*C*H$_2$Ph), 73.7 (*C*H$_2$Ph), 73.5 (*C*H$_2$Ph), 68.1 (C-6), 44.4 (C-2), 30.6 (C-7), 20.9 (OCO*C*H$_3$); HRMS (ESI): m/z [M+Na]$^+$ Calcd 621.2287; found: 621.2289.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(4-methylphenyl)thiomethyl-D-glucopyranosyl (4b): 87% yield; 1:3 α:β anomeric mixture; colorless oil; IR ($CHCl_3$, cm^{-1}): 1749, 1494, 1454, 1091, 699; ^1H NMR ($CDCl_3$, 400 MHz) for α-anomer: δ 7.51–7.05 (m, 19H, aromatic), 6.43 (bs, 1H, H-1), 4.96 (d, $J =$ 11.2 Hz, 1H, CH_AH$_B$Ph), 4.79 (d, $J = 10.4$ Hz, 1H, CH_AH$_B$Ph), 4.75–4.42 (m, 4H, the rest of the CH_2Ph), 3.95–3.62 (m, 5H, H-3, H-4, H-5, H-6$_a$ and H-6$_b$), 3.40 (d, $J = 13.2$ Hz, 1H, H-7$_a$), 2.58 (t, $J = 12.4$ Hz, 1H, H-7$_b$), 2.32 (s, 3H, ArCH_3), 2.95–2.18 (m, 1H, H-2), 2.05 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) for α-anomer: δ 169.0 (O*C*OCH$_3$), 138.1, 137.9, 137.7, 136.2, 131.8, 130.6, 129.7, 128.4, 128.3, 127.9, 127.8, 127.7 (aromatic), 92.0 (C-1), 78.9 (C-4), 78.8 (C-3), 75.3 (C-5), 74.9 (*C*H$_2$Ph), 73.5 (*C*H$_2$Ph), 73.0 (*C*H$_2$Ph), 68.1 (C-6), 44.3 (C-2), 31.4 (C-7), 20.9 (OCO*C*H$_3$), 20.8 (Ar*C*H$_3$); ^1H NMR ($CDCl_3$, 400 MHz) for β-anomer: δ 5.68 (d, $J = 8.8$ Hz, 1H, H-1), 3.27 (d, $J = 11.6$ Hz, 1H, H-7$_a$), 3.15 (d, $J = 12.8$ Hz, H-7$_b$), 1.98 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) for β-anomer: δ 169.0 (O*C*OCH$_3$), 137.8, 136.5, 132.9, 129.7, 128.4, 128.5, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6 (aromatic), 93.1 (C-1), 80.3 (C-4), 79.8 (C-3), 75.4 (C-5), 75.2 (*C*H$_2$Ph), 74.6 (*C*H$_2$Ph), 73.4 (*C*H$_2$Ph), 46.1 (C-2), 32.1 (C-7), 20.9 (OCO*C*H$_3$) 20.8 (Ar*C*H$_3$); HRMS (ESI): m/z [M+Na]$^+$ Calcd 635.2444; found: 635.2444.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(2-methylphenyl)thiomethyl-D-glucopyranosyl (4c): 87% yield; 1:3 α:β anomeric mixture; colorless oil; IR ($CHCl_3$, cm^{-1}): 1752, 1496, 1455, 1130, 698; ^1H NMR ($CDCl_3$, 400 MHz) for β-anomer: δ 7.45–7.05 (m, 19H, aromatic), 5.70 (d, J = 8.8 Hz, 1H, H-1), 4.94 (d, J = 10.8 Hz, 1H, CH_AH$_B$Ph), 4.80 (d, J = 10.4 Hz, 1H, CH_AH$_B$Ph), 4.75–4.40 (m, 4H, the rest of the CH_2Ph), 3.95–3.55 (m, 5H, H-3, H-4, H-5, H-6$_a$ and H-6$_b$), 3.24 (d, J = 10.8 Hz, 1H, H-7$_a$), 3.17 (d, J = 12.8 Hz, 1H, H-7$_b$), 2.40 (s, 3H, ArCH_3), 2.30–2.21 (m, 1H, H-2), 2.00 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) for β-anomer: δ 169.0 (O*C*OCH$_3$), 138.0, 137.9, 137.8, 135.8, 130.2, 128.4, 128.3, 128.0, 127.9, 127.8, 126.5, 126.1 (aromatic), 93.2 (C-1), 80.5 (C-4), 79.0 (C-3), 75.4 (C-5), 75.4 (*C*H$_2$Ph), 74.7 (*C*H$_2$Ph), 73.5 (*C*H$_2$Ph), 68.1 (C-6), 45.9 (C-2), 30.6 (C-7), 20.9 (OCO*C*H$_3$), 20.5 (Ar*C*H$_3$); ^1H NMR ($CDCl_3$, 400 MHz) for α-anomer: δ 6.40 (bs, 1H, H-1), 4.98 (d, J = 10.8 Hz, 1H, CH_AH$_B$Ph), 3.41 (d, J = 13.2 Hz, 1H, H-7$_a$), 2.56 (t, J = 12.2 Hz, 1H, H-7$_b$), 2.32 (s, 3H, ArCH_3), 2.06 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) for α-anomer: δ 169.0 (O*C*OCH$_3$), 137.9, 137.8, 137.4, 134.9, 129.0, 128.5, 127.7, 127.6, 127.4, 126.5, 126.4, 125.6 (aromatic), 92.0 (C-1), 80.3 (C-4), 78.9 (C-3), 75.4 (C-5), 74.9 (*C*H$_2$Ph), 73.6 (*C*H$_2$Ph), 73.0 (*C*H$_2$Ph), 68.1 (C-6), 44.2 (C-2), 29.7 (C-7), 20.9 (O*C*OCH$_3$), 20.3 (Ar*C*H$_3$); HRMS (ESI): m/z [M+Na]$^+$ Calcd 635.2444; found: 635.2444.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(4-*tert*-butylphenyl)thiomethyl-D-glucopyranosyl (4d): 93% yield; 1:3 α:β anomeric mixture; colorless oil; IR ($CHCl_3$, cm^{-1}): 1750, 1498, 1454, 1130, 698; ^1H NMR ($CDCl_3$, 400 MHz) for β-anomer: δ 7.45–7.21 (m, 19H, aromatic), 5.67 (d, J = 8.8 Hz, 1H, H-1), 4.92 (d, J = 10.8 Hz, 1H, CH_AH$_B$Ph), 4.80 (d, J = 10.4 Hz, 1H, CH_AH$_B$Ph), 4.75–4.38 (m, 4H, the rest of the CH_2Ph), 3.92–3.55 (m, 5H, H-3, H-4, H-5, H-6$_a$ and H-6$_b$), 3.29 (d, J = 12.0 Hz, 1H, H-7$_a$), 3.20–3.11 (m, 1H, H-7$_b$), 2.37–2.18 (m, 1H, H-2), 1.96 (s, 3H, OCOCH_3), 1.28 (s, 9H, ArC(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) for β-anomer: δ 169.0 (O*C*OCH$_3$), 149.3, 142.2, 138.1, 137.9, 137.7, 130.2, 129.4, 128.5, 128.4, 128.3, 128.0, 127.8, 126.0 (aromatic), 93.2 (C-1), 80.6 (C-4), 80.4 (C-3), 75.9 (C-5), 75.3 (*C*H$_2$Ph), 74.9 (*C*H$_2$Ph), 74.2 (*C*H$_2$Ph), 70.6 (C-6), 44.6 (C-2), 34.4 (Ar*C*(CH$_3$)$_3$), 32.0 (C-7), 31.2 (ArC(*C*H$_3$)$_3$), 20.9 (OCO*C*H$_3$); ^1H NMR ($CDCl_3$, 400 MHz) for α-anomer: δ 6.42 (bs, 1H, H-1), 4.97 (d, J = 11.2 Hz, 1H, CH_AH$_B$Ph), 3.45 (d, J = 13.2 Hz, 1H, H-7$_a$), 2.57 (t, J = 12.2 Hz, 1H, H-7$_b$), 2.04 (s, 3H, OCOCH_3), 1.30 (s, 9H, ArC(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) for α-anomer: δ 168.8 (O*C*OCH$_3$), 149.7, 138.2, 138.1, 137.9, 133.1, 132.0, 131.2, 128.8, 128.3, 128.0, 127.7, 127.6, 126.0, 125.8 (aromatic), 92.1 (C-1), 80.4 (C-4), 79.0 (C-4), 75.5 (C-5), 75.2 (*C*H$_2$Ph), 74.6 (*C*H$_2$Ph), 73.6 (*C*H$_2$Ph), 68.3 (C-6), 44.6 (C-2), 36.6 (Ar*C*CH$_3$), 32.0 (C-7), 31.3 (ArC(*C*H$_3$)$_3$), 20.9 (OCO*C*H$_3$); 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*-(2-naphtalene)thiomethyl-D-glucopyranosyl (4f): 86% yield; 1:3 α:β anomeric mixture; yellow oil; IR ($CHCl_3$, cm^{-1}): 1723, 1497, 1453, 1130, 695; ^1H NMR ($CDCl_3$, 400 MHz)

for β-anomer: δ 7.85–7.12 (m, 22H, aromatic), 5.72 (d, J = 8.8 Hz, 1H, H-1), 4.94 (d, J = 10.8 Hz, 1H, CH_AH$_B$Ph), 4.79 (d, J = 10.4 Hz, 1H, CH_AH$_B$Ph), 4.74–4.42 (m, 4H, the rest of CH_2Ph), 3.95–3.51 (m, 5H, H-3, H-4, H-5, H-6$_a$ and H-6$_b$), 3.34 (d, J = 13.2 Hz, 1H, H-7$_a$), 3.26 (d, J = 12.8 Hz, 1H, H-7$_b$), 2.39–2.24 (m, 1H, H-2), 1.90 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) for β-anomer: δ 169.1 (O*C*OCH$_3$), 138.0, 137.9, 134.1, 133.7, 133.1, 131.8, 128.4, 128.3, 127.8, 127.7, 127.1, 126.6, 125.8 (aromatic), 93.2 (C-1), 80.4 (C-4), 79.0 (C-3), 75.4 (C-5), 74.9 (*C*H$_2$Ph), 73.6 (*C*H$_2$Ph), 73.1 (C-6), 46.0 (C-2), 31.2 (C-7), 20.9 (OCO*C*H$_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) for α-anomer: δ 6.46 (bs, 1H, H-1), 5.01 (d, J = 11.2 Hz, 1H, CH_AH$_B$Ph), 2.70–2.59 (m, 1H, H-7$_b$), 2.05 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) for α-anomer: δ 169.1 (O*C*OCH$_3$), 138.0, 137.9, 134.1, 133.7, 133.1, 131.8, 128.4, 128.3, 127.8, 127.7, 127.1, 126.6, 125.8 (aromatic), 92.0 (C-1), 80.2 (C-4), 79.0 (C-3), 75.3 (C-5), 74.7 (*C*H$_2$Ph), 73.5 (*C*H$_2$Ph), 73.1 (C-6), 44.4 (C-2), 30.4 (C-7), 20.9 (OCO*C*H$_3$); HRMS (ESI): m/z [M+Na]$^+$ Calcd 671.2444; found: 671.2439.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-phenylthiomethyl-α-D-mannopyranosyl (9a): 95% yield, colorless oil; $[\alpha]_D$ = +49.6 (c 0.5, $CHCl_3$); IR (neat, cm^{-1}): 1749, 1496, 1454, 1363, 1096, 1025, 695; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.50–7.10 (m, 20H, aromatic), 6.44 (s, 1H, H-1), 4.83 (d, J = 10.4 Hz, 1H, CH_AH$_B$Ph), 4.64 (d, J = 12.0 Hz, 1H, CH_AH$_B$Ph), 4.55–4.35 (m, 4H, the rest of the CH_2Ph), 4.10–3.96 (m, 1H, H-3), 3.88–3.72 (m, 3H, H-5, H-4 and H-6$_a$), 3.65 (d, J = 10.4 Hz, 1H, H-6$_b$), 3.52 (d, J = 14.0 Hz, 1H, H-7$_a$), 2.90–2.78 (m, 1H, H-7$_b$), 2.45–2.30 (m, 1H, H-2), 2.04 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0 (O*C*OCH$_3$), 138.1, 138.0, 137.9, 135.5, 130.2, 128.9, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 126.4 (aromatic), 93.3 (C-1), 78.3 (C-3), 75.0 (*C*H$_2$Ph), 73.9 (C-4), 73.6 (*C*H$_2$Ph), 73.5 (*C*H$_2$Ph), 71.8 (C-5), 68.5 (C-6), 41.7 (C-2), 29.7 (C-7), 21.0 (OCO*C*H$_3$); HRMS (ESI): m/z [M+Na]$^+$ Calcd 621.2287; found 621.2287.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(4-methylphenyl)thiomethyl-α-D-mannopyranosyl (9b): 80% yield; colorless oil; $[\alpha]_D$ = +19.9 (c 0.5, $CHCl_3$); IR (neat, cm^{-1}): 1749, 1494, 1454, 1367, 1094, 1026, 697; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45–6.95 (m, 19H, aromatic), 6.43 (s, 1H, H-1), 4.81 (d, J = 10.8 Hz, 1H, CH_AH$_B$Ph), 4.62 (d, J = 12.4 Hz, 1H, CH_AH$_B$Ph), 4.60–4.30 (m, 4H, the rest of the CH_2Ph), 4.01–3.90 (m, 1H, H-3), 3.85–3.55 (m, 4H, H-5, H-4, H-6$_a$ and H-6$_b$), 3.44 (d, J = 13.6 Hz, 1H, H-7$_a$), 2.80–2.72 (m, 1H, H-7$_b$), 2.40–2.23 (m, 4H, H-2 and ArCH_3), 2.02 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0 (O*C*OCH$_3$), 138.2, 138.1, 137.9, 136.7, 131.7, 131.2, 129.8, 128.4, 128.4, 128.3, 128.0, 127.8, 127.7, 127.7, 127.6, 127.5 (aromatic), 93.4 (C-1), 78.3 (C-3), 75.0 (*C*H$_2$Ph), 73.9 (C-4), 73.6 (*C*H$_2$Ph), 73.5 (*C*H$_2$Ph), 71.5 (C-5), 68.6 (C-6), 41.6 (C-2), 30.5 (C-7), 21.1 (Ar*C*H$_3$), 21.0 (OCO*C*H$_3$); HRMS (ESI): m/z [M+Na]$^+$ Calcd 635.2443; found 635.2446.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(2-methylphenyl)thiomethyl-α-D-mannopyranosyl (9c): 93% yield; colorless oil; $[\alpha]_D$ = +23.0 (c 0.5,

$CHCl_3$); IR (neat, cm^{-1}): 1749, 1496, 1454, 1366, 1098, 1026, 697; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50–6.90 (m, 19H, aromatic), 6.45 (s, 1H, H-1), 4.83 (d, $J = 10.4$ Hz, 1H, CH_AH$_B$Ph), 4.63 (d, $J = 12.0$ Hz, 1H, CH_AH$_B$Ph), 4.60–4.35 (m, 4H, the rest of the CH_2Ph), 4.10–3.94 (m, 1H, H-3), 3.90–3.70 (m, 3H, H-4, H-5 and H-6$_a$), 3.64 (d, $J = 10.0$ Hz, 1H, H-6$_b$), 3.48 (d, $J = 13.2$ Hz, 1H, H-7$_a$), 2.88–2.76 (m, 1H, H-7$_b$), 2.45–2.20 (m, 4H, H-2 and ArCH_3), 2.03 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0 (O*C*OCH$_3$), 138.6, 138.1, 138.0, 137.9, 134.7, 130.3, 129.2, 128.4, 128.4, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 127.5, 126.4, 126.2 (aromatic), 93.3 (C-1), 78.4 (C-3), 75.1 (*C*H$_2$Ph), 74.0 (C-4), 73.6 (*C*H$_2$Ph), 73.5 (*C*H$_2$Ph), 71.8 (C-5), 68.5 (C-6), 41.6 (C-2), 28.7 (C-7), 21.1 (Ar*C*H$_3$), 20.4 (OCO*C*H$_3$); HRMS (ESI): m/z [M+Na]$^+$ Calcd 635.2443; found 635.2438.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(4-*tert*-butylphenyl)thio methyl-α-D-mannopyranosyl (9d): 93% yield; colorless oil; $[\alpha]_D = +25.8$ (*c* 0.5, $CHCl_3$); IR (neat, cm^{-1}): 1750, 1496, 1454, 1364, 1099, 1025, 697; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.45–7.05 (m, 19H, aromatic), 6.42 (s, 1H, H-1), 4.82 (d, $J = 10.4$ Hz, 1H, CH_AH$_B$Ph), 4.62 (d, $J = 12.0$ Hz, 1H, CH_AH$_B$Ph), 4.55–4.30 (m, 4H, the rest of the CH_2Ph), 4.04–3.91 (m, 1H, H-3), 3.85–3.72 (m, 3H, H-5, H-4 and H-6$_a$), 3.64 (d, $J = 10.4$ Hz, 1H, H-6$_b$), 3.46 (d, $J = 14.0$ Hz, 1H, H-7$_a$), 2.81–2.75 (m, 1H, H-7$_b$), 2.45–2.25 (m, 1H, H-2), 2.03 (s, 3H, OCOCH_3), 1.27 (s, 9H, (ArC(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0 (O*C*OCH$_3$), 149.8, 138.2, 138.1, 137.9, 132.0, 130.5, 128.4, 128.4, 128.0, 127.8, 127.7, 127.7, 127.6, 127.6, 126.0 (aromatic), 93.4 (C-1), 78.3 (C-3), 75.0 (*C*H$_2$Ph), 73.9 (C-4), 73.6 (*C*H$_2$Ph), 73.5 (*C*H$_2$Ph), 71.5 (C-5), 68.6 (C-6), 41.7 (C-2), 34.4 (Ar*C*(CH$_3$)$_3$), 31.2 (ArC(*C*H$_3$)$_3$), 30.2 (C-7), 21.1 (OCO*C*H$_3$); HRMS (ESI): m/z [M+Na]$^+$ Calcd 677.2913; found 677.2910.

1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(4-methoxyphenyl)thiom ethyl-α-D-mannopyranosyl (9e): 78% yield; colorless oil; $[\alpha]_D = +12.0$ (*c* 0.5, $CHCl_3$); IR (neat, cm^{-1}): 1746, 1591, 1493, 1454, 1366, 1096, 1026, 697; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50–7.05 (m, 17H, aromatic), 6.79 (d, $J = 8.4$ Hz, 2H, aromatic), 6.45 (s, 1H, H-1), 4.80 (d, $J = 10.8$ Hz, 1H, CH_AH$_B$Ph), 4.61 (d, $J = 12.0$ Hz, 1H, CH_AH$_B$Ph), 4.60–4.47 (m, 2H, 2 × CH$_A$$H_B$Ph), 4.35 (d, $J = 11.4$ Hz, 1H, CH_AH$_B$Ph), 4.26 (d, $J = 11.4$ Hz, 1H, CH$_A$$H_B$Ph), 4.05–3.90 (m, 1H, H-3), 3.85–3.70 (m, 6H, H-5, H-4, ArOCH_3 and H-6$_a$), 3.63 (d, $J = 10.4$ Hz, 1H, H-6$_b$), 3.34 (d, $J = 14.0$ Hz, 1H, H-7$_a$), 2.84–2.62 (m, 1H, H-7$_b$), 2.36–2.24 (m, 1H, H-2), 2.03 (s, 3H, OCOCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.0 (O*C*OCH$_3$), 159.2, 138.1, 138.1, 137.9, 134.2, 128.4, 128.4, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.5, 125.6, 114.6 (aromatic), 93.4 (C-1), 78.3 (C-3), 75.1 (*C*H$_2$Ph), 73.9 (C-4), 73.6 (*C*H$_2$Ph), 73.5 (*C*H$_2$Ph), 71.2 (C-5), 68.6 (C-6), 55.3 (ArO*C*H$_3$), 41.3 (C-2), 31.7 (C-7), 21.0 (OCO*C*H$_3$); HRMS (ESI): m/z [M+Na]$^+$ Calcd 651.2392; found 651.2394.

General procedure for the synthesis of the thiochromans

A sulfide, **4a–f** or **9a–e** (0.69 mmol), was dissolved in dry dichloromethane (3 mL) under an atmosphere of nitrogen and stirred together with 4Å molecular sieves at rt for 1 h. The mixture was cooled down to 0°C and then treated dropwise with $BF_3{\cdot}Et_2O$ (1 mL of 48% BF_3 solution in diethylether, 8.02 mmol). After stirring at this temperature for 5 min, Et_3N (0.7 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. 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/petroleum ether, 1:9) to yield the corresponding thiochromans:

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (5a): 69% yield; white solid; mp 91–95°C; $[\alpha]_D = -125.0$ (*c* 0.1, $CHCl_3$); IR (neat, cm^{-1}): 1452, 1082, 694; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.53 (d, $J = 7.2$ Hz, 1H, aromatic), 7.42–7.30 (m, 13H, aromatic), 7.13–7.03 (m, 5H, aromatic), 5.13 (d, $J = 5.6$ Hz, 1H, H-1), 4.96 (d, $J = 11.0$ Hz, 1H, CH_AH_BPh), 4.85 (d, $J = 11.0$ Hz, 1H, CH_AH_BPh), 4.78 (d, $J = 10.8$ Hz, 1H, CH_AH_BPh), 4.70 (d, $J = 12.0$ Hz, 1H, CH_AH_BPh), 4.60–4.58 (m, 2H, the rest of the CH_AH_BPh), 4.03 (t, $J = 13.2$ Hz, 1H, H-3), 3.88–3.69 (m, 3H, H-4, H-6_a and H-6_b), 3.47 (d, $J = 9.2$ Hz, 1H, H-5), 3.35 (bd, $J = 13.2$ Hz, 1H, H-7_a), 3.19 (dd, $J = 3.6$ and 13.6 Hz, 1H, H-7_b), 2.62–2.50 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.7, 138.0, 134.4, 131.4, 128.5, 127.9, 127.8, 127.7, 127.6, 126.3, 124.8 (aromatic), 80.0 (C-4), 78.7 (C-3), 75.9 (CH_2Ph), 74.8 (CH_2Ph), 73.5 (CH_2Ph), 72.8 (C-5), 72.4 (C-1), 68.9 (C-6), 38.4 (C-2), 26.4 (C-7); HRMS (ESI): m/z $[M+H]^+$ Calcd 539.2256; found: 539.2259.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (5b): 71% yield; white solid; mp 105–107°C; $[\alpha]_D = +91.0$ (*c* 0.1, $CHCl_3$); IR (neat, cm^{-1}): 1453, 1108, 695; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.45–7.20 (m, 14H, aromatic), 7.18–7.06 (m, 2H, aromatic), 7.02–6.88 (m, 2H, aromatic), 5.09 (d, $J = 5.6$ Hz, 1H, H-1), 4.95 (d, $J = 11.0$ Hz, 1H, CH_AH_BPh), 4.85 (d, $J = 11.0$ Hz, 1H, CH_AH_BPh), 4.78 (d, $J = 10.8$ Hz, 1H, CH_AH_BPh), 4.71 (d, $J = 9.2$ Hz, 1H, CH_AH_BPh), 4.60–4.48 (m, 2H, the rest of the CH_AH_BPh), 4.03 (t, $J = 9.8$ Hz, 1H, H-3), 3.80–3.68 (m, 3H, H-4, H-6_a and H-6_b), 3.59–3.49 (m, 1H, H-5), 3.33 (bd, $J = 11.2$ Hz, 1H, H-7_a), 3.18 (dd, $J = 3.8$ Hz and 13.6 Hz, 1H, H-7_b), 2.60–2.49 (m, 1H, H-2), 2.23 (s, 3H, $ArCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.1, 134.5, 131.2, 130.6, 128.6, 128.5, 128.4, 128.0, 127.8, 127.7, 127.6, 126.2 (aromatic), 80.1 (C-4), 78.8 (C-3), 75.9 (CH_2Ph), 74.8 (CH_2Ph), 73.4 (CH_2Ph), 72.8 (C-5), 72.5, (C-1) 69.1 (C-6), 38.6 (C-2), 26.5 (C-7), 21.0 ($ArCH_3$) HRMS (ESI): m/z $[M+H]^+$ Calcd 553.2412; found: 553.2410.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (5c): 73% yield; white solid; mp 119–121°C; $[\alpha]_D = +127.0$ (*c* 0.1, $CHCl_3$); IR (neat, cm^{-1}): 1496, 1406, 1140, 694; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50–7.20 (m, 14H, aromatic), 7.18–7.19 (m, 2H, aromatic), 7.05–6.95 (m, 2H, aromatic), 5.17 (d, $J = 5.2$ Hz, 1H, H-1), 4.97 (d, $J = 11.0$ Hz, 1H, CH_AH_BPh), 4.88 (d, $J = 11.0$ Hz, 1H, CH_AH_BPh), 4.79 (d, $J = 10.8$ Hz, 1H, CH_AH_BPh), 4.71 (d, $J = 12.0$ Hz, 1H, CH_AH_BPh), 4.62–4.48 (m, 2H, the rest of the CH_AH_BPh), 4.04 (t, $J = 9.8$ Hz, 1H, H-3), 3.80–3.60 (m, 3H, H-4, H-6_a and H-6_b), 3.47 (d, $J = 9.2$ Hz, 1H, H-5), 3.38–3.20 (m, 2H, H-7_a and H-7_b), 2.60–2.52 (m, 1H, H-2), 2.23 (s, 3H $ArCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.7, 138.0, 137.9, 134.3, 133.9, 131.4, 128.7, 128.5, 128.4, 127.9, 127.8, 127.7, 125.0, 124.0 (aromatic), 79.9 (C-4), 78.6 (C-3), 75.8 (CH_2Ph), 74.7 (CH_2Ph), 73.4 (CH_2Ph), 72.7 (C-5), 72.6 (C-1), 68.8 (C-6), 37.9 (C-7), 26.0 (C-2), 20.1 ($ArCH_3$); HRMS (ESI): m/z $[M+H]^+$ Calcd 553.2412; found: 553.2415.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-*tert*-butyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (5d): 69% yield; white solid; mp 157–159°C; $[\alpha]_D = +92.0$ (*c* 0.1, $CHCl_3$); IR (neat, cm^{-1}): 1478, 1134, 1103, 697; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.61 (s, 1H, aromatic), 7.42–7.21 (m, 13H, aromatic), 7.18–7.07 (m, 3H, aromatic), 6.97 (d, $J =$ 8 Hz, 1H, aromatic), 5.13 (d, $J = 5.6$ Hz, 1H, H-1), 4.96 (d, $J = 11.2$ Hz, 1H, CH_AH_BPh), 4.87 (d, $J = 11.2$ Hz, 1H, CH_AH_BPh), 4.77 (d, $J = 10.8$ Hz, 1H, CH_AH_BPh), 4.68 (d, $J = 12.0$ Hz, 1H, CH_AH_BPh), 4.56 (d, $J = 12.0$ Hz, 1H, CH_AH_BPh), 4.48 (d, $J = 10.8$ Hz, 1H, CH_AH_BPh), 4.04 (t, $J = 9.8$ Hz, 1H, H-3), 3.79–3.18 (m, 3H, H-4, H-6_a and H-6_b), 3.55–3.48 (m, 1H, H-5), 3.34 (bd, $J =$ 13.6 Hz, 1H, H-7_a), 3.18 (dd, $J = 3.6$ and 13.2 Hz, 1H, H-7_b), 2.10–2.08 (m, 1H, H-2), 1.24 (s, 9H, $ArC(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.0, 138.8, 138.0, 137.9, 130.7, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 125.9, 124.8, 124.6 (aromatic), 80.3 (C-4), 78.8 (C-3), 75.9 (CH_2Ph), 74.9 (CH_2Ph), 73.6 (CH_2Ph), 73.0 (C-5), 72.7 (C-1), 69.1 (C-6), 38.7 (C-7), 34.4 ($ArC(CH_3)_3$), 31.2 ($ArC(CH_3)_3$), 26.3 (C-2); HRMS (ESI): m/z $[M+H]^+$ Calcd 595.2882; found: 595.2880.

(2*R*,3*S*,4*R*,4a*S*,10b*S*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methoxy-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (5e): 70% yield; white solid; mp 130–132°C; $[\alpha]_D = +111.0$ (*c* 0.1, $CHCl_3$); IR (neat, cm^{-1}): 1472, 1134, 1103, 698; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.42–7.20 (m, 13H, aromatic), 7.17–7.11 (m, 3H, aromatic), 6.96 (d, $J = 8.4$ Hz, 1H, aromatic), 6.71 (d, $J = 8.4$ Hz, 1H, aromatic), 5.09 (d, $J = 5.6$ Hz, 1H, H-1), 4.96 (d, $J =$ 11.0 Hz, 1H, CH_AH_BPh), 4.87 (d, $J = 11.0$ Hz, 1H, CH_AH_BPh), 4.79 (d, $J =$ 10.8 Hz, 1H, CH_AH_BPh), 4.66 (d, $J = 12.0$ Hz, 1H, CH_AH_BPh), 4.52 (m, 2H, the rest of the CH_AH_BPh), 4.05 (t, $J = 9.8$ Hz, 1H, H-3), 3.80–3.72 (m, 3H, H-4, H-6_a and H-6_b), 3.66 (s, 3H, $ArOCH_3$), 3.53 (m, 1H, H-5), 3.33 (bd, $J =$ 13.2 Hz, 1H, H-7_a), 3.18 (dd, $J = 3.6$ and 13.6 Hz, 1H, H-7_b), 2.62–2.51 (m, 1H,

H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.5, 138.7, 138.0, 132.5, 128.4, 128.3, 128.0, 127.7, 127.3, 124.8, 115.2, 112.0 (aromatic), 80.2 (C-4), 78.8 (C-3), 75.9 (CH_2Ph), 74.8 (CH_2Ph), 73.6 (CH_2Ph), 73.0 (C-5), 72.6 (C-1), 69.2 (C-6), 55.3 ($ArOCH_3$), 38.6 (C-7), 26.5 (C-2); HRMS (ESI): m/z $[M+H]^+$ Calcd 569.2361; found: 569.2354.

(2*R*,3*S*,4*R*,4a*S*,10b*S*) - 3,4 - bis(benzyloxy) - 2 - (benzyloxymethyl) - 2, 3,4,4a,5,12c-hexahydro-1*H*-dibenzo[*c,f*]thiochromeno[4,3-*b*]pyran (5f): 68% yield; yellow solid; mp 154–156°C; $[\alpha]_D = +91.0$ (c 0.1, $CHCl_3$); IR (neat, cm^{-1}): 1496, 1363, 1124, 1071, 697; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, J = 8.4 Hz, 1H, aromatic), 7.69 (d, J = 7.6 Hz, 1H, aromatic), 7.57 (d, J = 8.8 Hz, 1H, aromatic), 7.49–7.18 (m, 17H, aromatic), 7.10 (d, J = 8.4 Hz, 1H, aromatic), 4.98 (d, J = 10.8 Hz, 1H, H-1), 4.96–4.72 (m, 2H, CH_AH_BPh), 4.69 (d, J = 11.0 Hz, 1H, CH_AH_BPh), 4.61 (d, J = 11.0 Hz, 1H, CH_AH_BPh), 4.54 (d, J = 11.6 Hz, CH_AH_BPh), 4.48 (d, J = 11.6 Hz, CH_AH_BPh), 4.00–3.91 (m, 1H, H-3), 3.85 (d, J = 10.4 Hz, 1H, H-6_a), 3.80–3.63 (m, 2H, H-4 and H-6_b), 3.60–3.52 (m, 1H, H-5), 3.12 (d, J = 12.4 Hz, 1H, H-7_a), 2.73 (t, J = 12.4 Hz, 1H, H-7_b), 2.65–2.50 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.0, 128.7, 128.6, 128.5, 128.5, 128.2, 128.0, 127.8, 127.5, 126.2, 125.6, 125.2, 124.5 (aromatic), 85.0 (C-4), 80.4 (C-3), 80.3 (C-1), 76.2 (CH_2Ph), 75.3 (CH_2Ph), 75.0 (CH_2Ph), 73.4 (C-5), 69.6 (C-6), 46.3 (C-7), 25.3 (C-2); HRMS (ESI): m/z $[M+H]^+$ Calcd 589.2412; found: 589.2402.

(2*R*,3*S*,4*R*,4a*R*,10b*R*) - 3,4 - bis(benzyloxy) - 2 - (benzyloxymethyl) - 2,3, 4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (10a): 75% yield; white solid; mp 87–89°C; $[\alpha]_D = +35.2$ (c 0.5, $CHCl_3$); IR (neat, cm^{-1}): 1454, 1361, 1075, 1010, 694; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45–6.95 (m, 19H, aromatic), 4.88 (d, J = 10.8 Hz, 1H, CH_AH_BPh), 4.75 (d, J = 11.6 Hz, 1H, CH_AH_BPh), 4.68–4.40 (m, 4H, the rest of the CH_2Ph), 4.35 (s, 1H, H-1), 4.00–3.85 (m, 1H, H-3), 3.80–3.55 (m, 4H, H-6_a, H-6_b, H-5 and H-4), 3.26 (t, J = 12.6 Hz, 1H, H-7a), 2.96 (bd, J = 12.4 Hz, 1H, H-7_b), 2.70–2.50 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.4, 138.3, 138.0, 134.1, 133.3, 131.2, 128.7, 128.5, 128.3, 128.3, 127.9, 127.8, 127.7, 127.6, 127.5, 126.4, 124.1 (aromatic), 82.9 (C-3), 79.9 (C-4), 75.1 (CH_2Ph), 74.6 (C-1), 74.3 (C-5), 73.4 (CH_2Ph), 71.3 (CH_2Ph), 69.4 (C-6), 39.0 (C-2), 21.3 (C-7); HRMS (ESI): m/z $[M+Na]^+$ Calcd 539.2256; found 539.2260.

(2*R*,3*S*,4*R*,4a*R*,10b*R*) - 3,4 - bis(benzyloxy) - 2 - (benzyloxymethyl) - 9 -methyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (10b): 83% yield; white solid; mp 101–103°C; $[\alpha]_D = +29.9$ (c 0.5, $CHCl_3$); IR (neat, cm^{-1}): 1485, 1455, 1369, 1072, 1027, 698; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45–6.90 (m, 18H, aromatic), 4.87 (d, J = 10.8 Hz, 1H, CH_AH_BPh), 4.74 (d, J = 11.6 Hz, 1H, CH_AH_BPh), 4.68–4.40 (m, 4H, the rest of the CH_2Ph), 4.31 (s, 1H, H-1), 4.00–3.85 (m, 1H, H-3), 3.82–3.55 (m, 4H, H-6_a, H-6_b, H-5 and H-4), 3.25 (t, J = 12.6 Hz, 1H, H-7_a), 2.94 (bd, J = 12.4 Hz, 1H, H-7_b), 2.70–2.50 (m, 1H, H-2), 2.27 (s, 3H, $ArCH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.3, 138.2, 138.0,

133.8, 130.9, 130.4, 129.8, 128.5, 128.4, 128.3, 128.0, 127.8, 127.7, 127.5, 126.2 (aromatic), 83.0 (C-3), 79.8 (C-4), 75.1 (CH$_2$Ph), 74.5 (C-1), 74.4 (C-5), 73.4 (CH$_2$Ph), 71.2 (CH$_2$Ph), 69.4 (C-6), 39.1 (C-2), 21.2 (C-7), 20.7 (ArCH$_3$); HRMS (ESI): m/z [M+Na]$^+$ Calcd 553.2413; found 553.2422.

(2*R*,3*S*,4*R*,4a*R*,10b*R*) - 3,4 - bis(benzyloxy) - 2 - (benzyloxymethyl) - 7 -methyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (10c): 94% yield; white solid; mp 82–84°C; $[\alpha]_D$ = +25.2 (c 0.5, CHCl$_3$); IR (neat, cm^{-1}): 1455, 1361, 1072, 1029, 696; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.50–6.90 (m, 18H, aromatic), 4.88 (d, J = 10.8 Hz, 1H, CH_AH$_B$Ph), 4.75 (d, J = 11.6 Hz, 1H, CH_AH$_B$Ph), 4.68–4.42 (m, 4H, the rest of the CH_2Ph), 4.37 (s, 1H, H-1), 4.40–3.85 (m, 1H, H-3), 3.81–3.55 (m, 4H, H-6$_a$, H-6$_b$, H-5 and H-4), 3.24 (t, J = 12.8 Hz, 1H, H-7$_a$), 3.03 (bd, J = 12.4 Hz, 1H, H-7$_b$), 2.70–2.50 (m, 1H, H-2), 2.25 (s, 3H, ArCH_3); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 138.3, 138.2, 138.0, 134.3, 133.4, 131.0, 130.8, 130.0, 128.5, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 127.5, 123.5 (aromatic), 82.8 (C-3), 79.8 (C-4), 75.1 (CH$_2$Ph), 74.7 (C-1), 74.5 (C-5), 73.4 (CH$_2$Ph), 71.2 (CH$_2$Ph), 69.4 (C-6), 38.5 (C-2), 21.2 (C-7), 19.3 (ArCH$_3$); HRMS (ESI): m/z [M+Na]$^+$ Calcd 553.2413; found 553.2411.

(2*R*,3*S*,4*R*,4a*R*,10b*R*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-*tert*-butyl-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (10d): 70% yield; white solid; mp 83–84°C; $[\alpha]_D$ = +32.4 (c 0.5, CHCl$_3$); IR (neat, cm^{-1}): 1454, 1361, 1072, 1030, 696; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.50–7.00 (m, 18H, aromatic), 4.91 (d, J = 10.4 Hz, 1H, CH_AH$_B$Ph), 4.77 (d, J = 11.6 Hz, 1H, CH_AH$_B$Ph), 4.70–4.45 (m, 4H, the rest of the CH_2Ph), 4.37 (s, 1H, H-1), 4.00–3.60 (m, 5H, H-3, H-6$_a$, H-6$_b$, H-5 and H-4), 3.29 (t, J = 12.6 Hz, 1H, H-7$_a$), 2.98 (bd, J = 12.4 Hz, 1H, H-7$_b$), 2.70–2.50 (m, 1H, H-2), 1.31 (s, 9H, (ArC(CH_3)$_3$); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 147.1, 138.3, 138.3, 138.0, 130.6, 130.6, 130.0, 128.4, 128.3, 128.2, 128.0, 127.7, 127.7, 127.7, 127.6, 127.4, 126.3, 126.0 (aromatic), 83.0 (C-3), 79.9 (C-4), 75.1 (CH$_2$Ph), 74.6 (C-1), 74.6 (C-5), 73.4 (CH$_2$Ph), 71.2 (CH$_2$Ph), 69.4 (C-6), 39.2 (C-2), 34.2 (ArC(CH$_3$)$_3$), 31.2 (ArC(CH$_3$)$_3$), 21.2 (C-7); HRMS (ESI): m/z [M+Na]$^+$ Calcd 595.2882; found 595.2888.

(2*R*,3*S*,4*R*,4a*R*,10b*R*)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methoxy-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran (10e): 92% yield; yellow solid; mp 106–108°C; $[\alpha]_D$ = +30.5 (c 0.5, CHCl$_3$); IR (neat, cm^{-1}): 1483, 1454, 1369, 1062, 1028, 698; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.50–7.10 (m, 15H, aromatic), 7.03 (d, J = 8.8 Hz, 1H, aromatic), 6.86 (s, 1H, aromatic) 6.78 (d, J = 8.4 Hz, 1H, aromatic), 4.87 (d, J = 10.4 Hz, 1H, CH_AH$_B$Ph), 4.75 (d, J = 11.6 Hz, 1H, CH_AH$_B$Ph), 4.68–4.40 (m, 4H, the rest of the CH_2Ph), 4.32 (s, 1H, H-1), 4.00–3.55 (m, 8H, H-3, ArOCH_3, H-6$_a$, H-6$_b$, H-5 and H-4), 3.24 (t, J = 12.6 Hz, 1H, H-7$_a$), 2.94 (bd, J = 12.4 Hz, 1H, H-7$_b$), 2.70–2.50 (m, 1H, H-2); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 156.7, 138.3, 138.2, 138.0, 132.0, 128.5, 128.3, 128.3, 128.0, 127.8, 127.7, 127.5, 127.3, 124.8, 117.6, 116.2 (aromatic), 82.9 (C-3), 79.9 (C-4), 75.1 (CH$_2$Ph), 74.5 (C-1 and C-5), 73.4 (CH$_2$Ph), 71.2

(*C*H_2Ph), 69.4 (C-6), 55.4 (ArO*C*H_3), 39.3 (C-2), 21.3 (C-7); HRMS (ESI): *m*/*z* [M+Na]$^+$ Calcd 569.2362; found 569.2357.

Sulfone 6

The sulphide **5a** (130 mg, 0.24 mmol) was added to a vigorously stirring suspension of wet alumina (650 mg wetted with 70 μL of water) and OXONE (1.19 g, 1.92 mmol) and the reaction mixture was stirred at rt overnight. After allowing the mixture to cool to rt, it was filtered to remove the adsorbent. Evaporation of the solvent and flash-chromatographic purification on silica gel (ethyl acetate/petroleum ether, 2:8) gave sulfone **6** in 78% yield; white solid; crystallization from the DCM-hexane solvent system gave clear crystals; mp 116–118°C; $[\alpha]_D = +53.0$ (*c* 0.1, $CHCl_3$); IR (neat, cm^{-1}): 1453, 1305, 1101, 696; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56 (d, $J = 8.4$ Hz, 1H, aromatic), 7.63–7.48 (m, 3H, aromatic), 7.40–7.20 (m, 13H, aromatic), 7.18–7.10 (m, 2H, aromatic), 5.19 (d, $J = 4.0$ Hz, 1H, H-1), 4.85 (d, $J = 10.6$ Hz, 1H, CH_AH$_B$Ph), 4.80 (d, $J = 10.6$ Hz, 1H, CH$_A$$H_B$Ph), 4.72 (d, $J = 11.2$ Hz, 1H, CH_AH$_B$Ph), 4.66 (d, $J = 12.0$ Hz, 1H, CH_AH$_B$Ph), 4.62–4.54 (m, 2H, the rest of the CH$_A$$H_B$Ph), 4.11–3.96 (m, 2H, H-3, H-4), 3.84 (m, 1H, H-5), 3.78–3.67 (m, 3H, H-6$_a$, H-6$_b$ and H-7$_a$), 3.42 (bd, $J = 14.4$ Hz, 1H, H-7$_b$), 2.95–2.80 (m, 1H, H-2); ^{13}C NMR: ($CDCl_3$, 100 MHz): δ 139.4, 138.1, 137.8, 137.6, 134.0, 132.9, 129.5, 128.5, 128.4, 128.3, 127.9, 127.8, 127.6, 123.7 (aromatic) 78.1 (C-3 and C-4), 74.3 (*C*H_2Ph), 74.1 (*C*H_2Ph), 74.0 (*C*H_2Ph), 73.4 (C-5), 69.4 (C-1), 68.2 (C-6), 49.3 (C-2), 39.5 (C-7); HRMS (ESI): *m*/*z* [M+Na]$^+$ Calcd 593.1974; found: 593.1740.

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