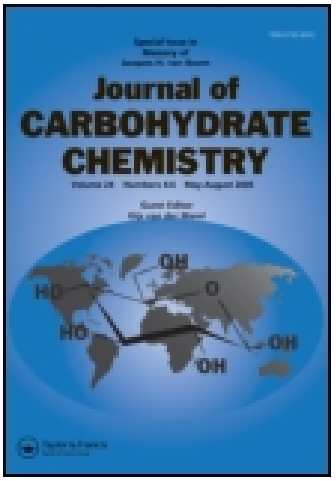

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New Carbohydrate-Derived S,S-Dioxothiochroman Derivatives and Their Unexpected Easy Epimerization at the Anomeric Position

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New Carbohydrate-Derived *S,S*-Dioxothiochroman Derivatives and Their Unexpected Easy Epimerization at the Anomeric Position

Henok H. Kinfe, Felix L. Makolo, Paseka T. Moshapo, and Zanele H. Phasha

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An efficient and stereoselective procedure is developed for high-yield preparation of novel *S,S*-dioxothiochroman carbohydrate derivatives **5a–e** from their corresponding sulfone epimers **3a–e** via anomeric epimerization in the presence of sodium hydride.

Keywords Dioxothiochroman; Epimerization; Sulfone

INTRODUCTION

Thiochromans, 3,4-dihydro-2*H*-1-benzothiopyrans, continue to attract significant interest from organic and medicinal chemists due to their presence as key components in biologically active compounds against cancer,[1] HIV,[2] malaria,[3] and bacteria,[4] as well as in the treatment of depression,[5] schizophrenia,[5a] Alzheimer's disease,[6] and Parkinson's disease.[5a] Moreover, the enhanced biological activity exhibited by thiochromans in comparison to their corresponding oxygen analogs[5b,7] (chromans) and the ease of derivatizing them into different analogs as shown in Scheme 1, thus generating libraries of compounds for structure-activity relationship studies, make thiochromans one of the sought-after compounds. Several strategies for the synthesis of

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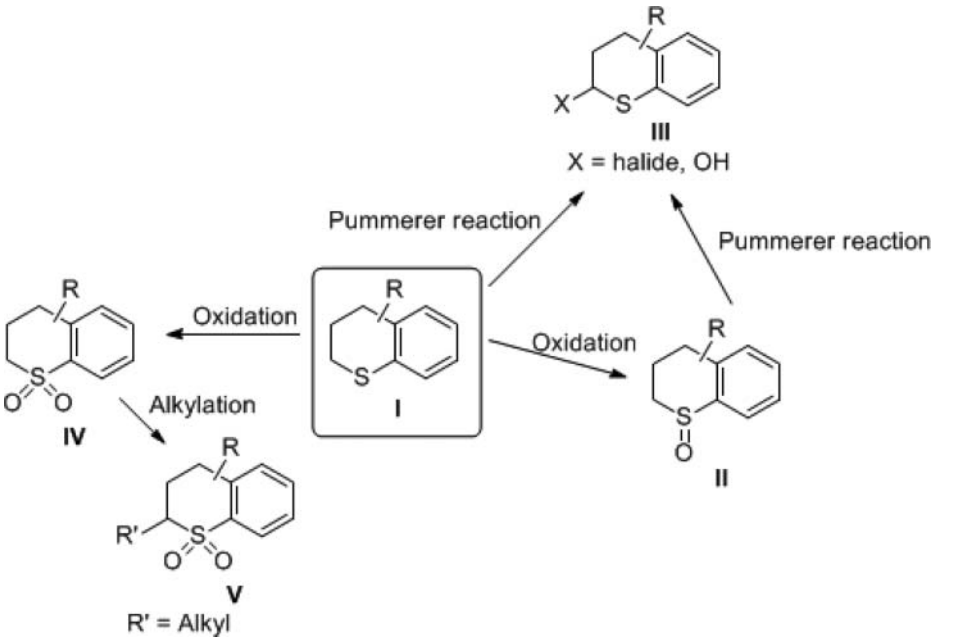
thiochromans, which include thio-Claisen rearrangement of allyl phenyl sulfides and stereoselective cycloaddition reactions, have been reported in the literature.[6b,8–19]



Scheme 1: Possible derivatization of thiochromans into useful synthetic intermediates.

We recently reported an efficient protocol for the diastereoselective preparation of carbohydrate-based thiochromans in which the orientation of the substituent at C-2 of a pyranosyl substrate induces the stereochemistry of the thiochroman products. More specifically, 1α,2α-aryl-*C*-glycoside **1** and 1β,2β-aryl-*C*-mannoside **2** were synthesized by this protocol (Fig. 1).[20] In this paper we report that the stereoselective access to these types of compounds can be expanded via the treatment of sulfone derivatives of the 1α,2α-aryl-*C*-glycoside **1** with sodium hydride.

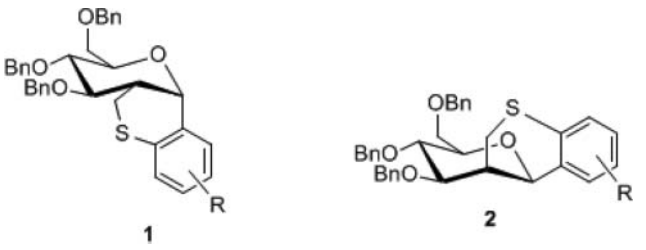
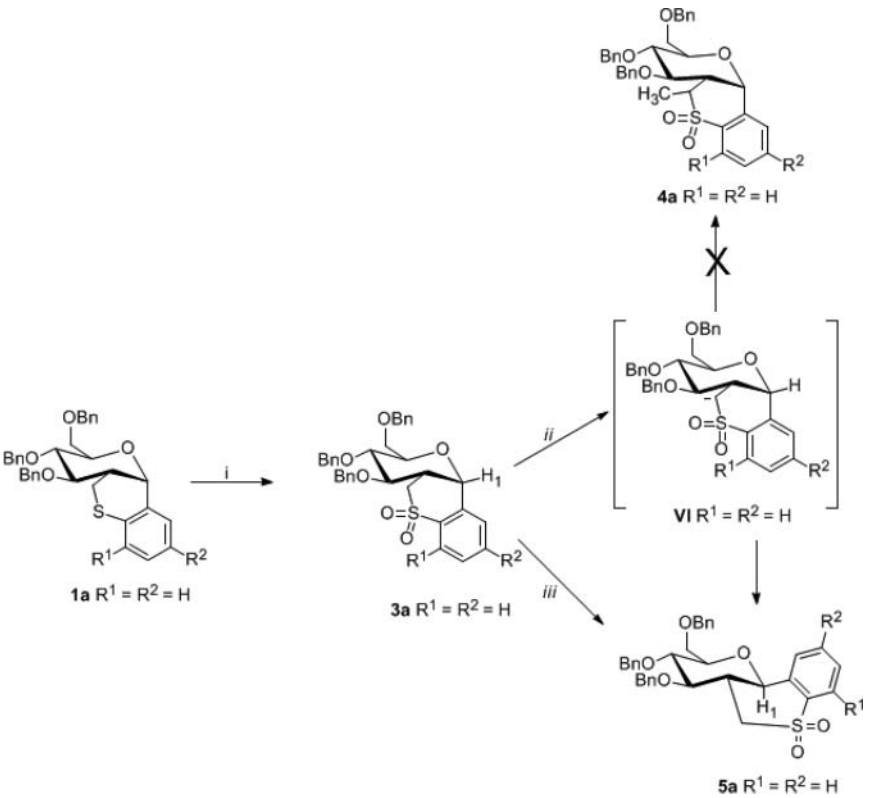


Figure 1: Structures of the carbohydrate-based thiochromans **1** and **2**.

RESULTS AND DISCUSSION

This discovery resulted from our attempts to synthesize derivatives of 1α,2α-aryl-*C*-glycoside **1** for structure-activity relationship studies against cancer (breast, colon, and prostate cancers). It was envisaged that oxidation of **1** would result in a sulfone derivative,[20] which, upon deprotonation of the acidic proton α to the sulfur with a base followed by treatment with an alkyl halide, would provide an alkylated product. Thus, sulfide **1a** was oxidized to sulfone **3a,**[20] which was then successively treated with sodium hydride and methyl iodide as an alkylating[21] agent in the hope of obtaining **4a** via deprotonation at H-7 as shown in Scheme 2. Thin layer chromatography (TLC) analysis of the reaction showed formation of a slightly more polar product relative to the starting sulfone. However, structural analysis of the new product confirmed the formation of the unexpected sulfone epimer **5a** instead of the alkylated sulfone **4a**. Carrying out the same reaction in the absence of methyl iodide resulted in the



Scheme 2: (*i*) Oxone, wet alumina, DCM, rt, 12 h, 69%; (*ii*) NaH, DMF, rt, 30 min followed with CH_3I, rt, 1 h, 68% (**5a**); (*iii*) NaH, DMF, rt, 15 min, 87%.

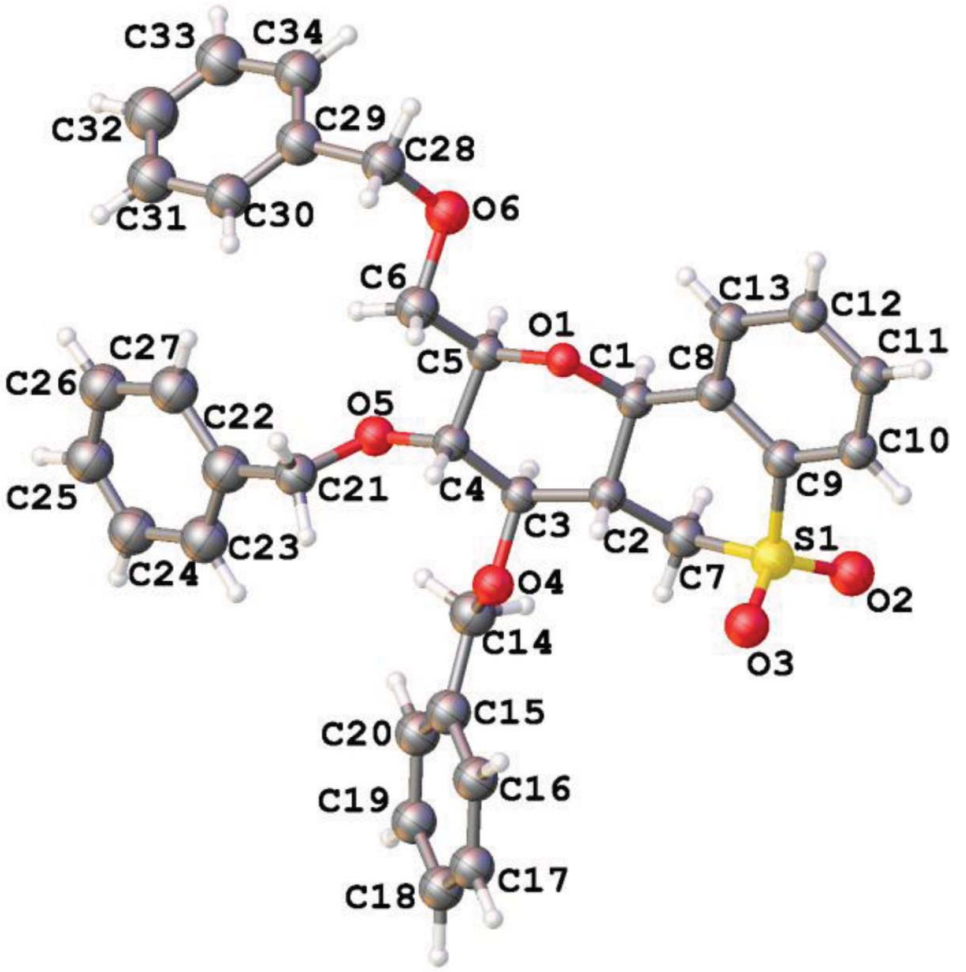


Figure 2: Single x-ray crystal structure of sulfone **5a** (color figure available online).

formation of the same epimer. The shift of the anomeric proton signal and increase in the $^{3}J_{\text{H-1,H-2}}$ coupling constant of the sulfone epimer **5a** from 4.0 Hz in sulfone **3a** to 10.4 Hz indicates a trans-diaxial relationship between H-1 and H-2, and this could be achieved if the configuration of the anomeric proton is α.[22] The absolute structure of the sulfone epimer **5a** was also determined using x-ray crystallography (Fig. 2).[23]

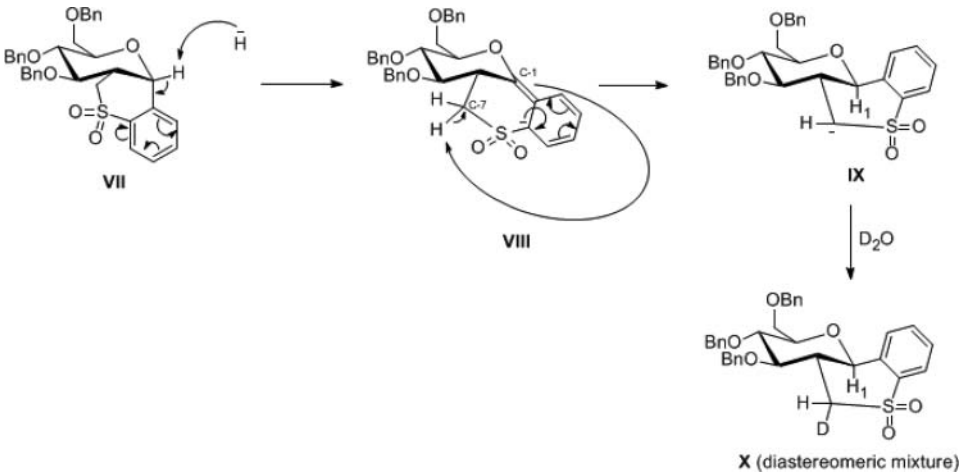
By varying the amount of NaH used, it was established that 1.5 equivalents are sufficient to fully epimerize the starting sulfone **3a** to **5a** in short reaction time at room temperature. Treatment of various sulfones **3b–e** (Table 1) in this way provided efficient access to the new sulfone epimers **5b–e**. In all cases

Table 1: Results of the oxidation of sulfide **1a–e** to sulfone **3a–e** and of the epimerization reaction

		Sulfone 3a–e		Sulfone epimer 5a–e	
Entry	Aromatic substituent	Product	% Yield	Product	% Yield
1	$R^1 = R^2 = H$	3a	69	5a	87
2	$R^1 = H$, $R^2 = CH_3$	3b	71	5b	88
3	$R^1 = CH_3$, $R^2 = H$	3c	73	5c	85
4	$R^1 = H$, $R^2 = Bu^t$	3d	69	5d	94
5	$R^1 = H$, $R^2 = OCH_3$	3e	70	5e	92

complete conversion of the starting sulfones to their corresponding epimers was achieved in short reaction time, and products were identified by ^1H and ^{13}C NMR spectroscopy after chromatographic purification.

The transformation from the starting sulfone to its epimer probably involves deprotonation at the benzylic (allylic) position relative to the sulfone, thus giving rise to the preferred resonance-stabilized anion **VIII** (Sch. 3) in contrast to the relatively less stabilized resonance anion **VI** from deprotonation at H-7 (Sch. 2). The possibility of both anions (**VI** and **VIII**) forming initially cannot be excluded but with time equilibrium moves to species **VIII,** which is then protonated at the anomeric center via internal or external hydrogen transfer from C-7. In this regard, the sp^2 hybridized anomeric center in **VIII** is protonated from the α side to form the equatorially substituted stable epimer in



Scheme 3: Proposed mechanism of the epimerization reaction via intramolecular deprotonation at C-7.

order to avoid the 1,3-diaxial strain of the phenyl group. Species **IX** is then protonated upon workup to give the epimerized product. To confirm which anion was finally trapped during the workup, the reaction was quenched with D_2O (Sch. 3). The ^{1}H NMR spectrum of the product so obtained indicated that the integrations of the H-7_a and H-7_b signals reduced by almost 50% while the integration of the H-1 signal remained intact (Sch. 3), supporting the formation of anion **IX** (via either inter- or intramolecular deprotonation). The decrease in the integration of H-7_a and H-7_b by 50% also indicates that compound **X** is a mixture of diastereomers.

CONCLUSION

In conclusion, we have demonstrated that access to new stereoisomers of the carbohydrate-based thiochroman derivatives could be achieved efficiently via epimerization at the anomeric center. Currently we are investigating the effect of stereochemistry on the biological activity of these compounds and results will be reported in due course.

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 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% sulphuric 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.

General Procedure for the Synthesis of Sulfones 3a–e

A sulfide **1a–e**[24] (0.28 mmol) was added to a vigorously stirring suspension of wet alumina (852 mg wetted with 90 μL of water) and OXONE® (1.4 g, 2.28 mmol) in DCM (5 mL). The reaction mixture was stirred at rt 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 corresponding sulfones **3a–e**.

(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydro-S,S-dioxothiochromeno[4,3-b]pyran (3a):

69% yield; white solid; mp 116–118°C; $[\alpha]_D = +53.0$ (c 0.1, $CHCl_3$); IR (neat, cm^{-1}): 1453, 1305, 1101, 696; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.92 (d, 1H, J = 7.6 Hz, Aromatic), 7.63–7.47 (m, 3H, Aromatic), 7.42–7.21 (m, 13H, Aromatic), 7.29–7.10 (m, 2H, Aromatic), 5.19 (d, 1H, J = 4.0 Hz, H-1), 4.90–4.78 (m, 2H, CH_2Ph), 4.74–4.62 (m, 2H, CH_2Ph), 4.59–4.48 (m, 2H, CH_2Ph), 4.10–3.98 (m, 2H, H-3, H-7_a), 3.84–3.66 (m, 4H, H-4, H-5, H-6_a, H-6_b) 3.42 (bd, 1H, J = 14.4 Hz, H-7_b), 2.93–2.84 (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-4), 77.3 (C-3) 74.3 (C-5), 74.1, 74.0, 73.4 (CH_2Ph), 69.4 (C-1), 68.2 (C-6), 49.3 (C-7), 39.5 (C-2). The spectroscopic data were in agreement with the literature.[20]

(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methyl-2,3,4,4a,5,10b-hexahydro-S,S-dioxothiochromeno[4,3-b]pyran (3b):

71% yield; white solid; mp 115–117°C; $[\alpha]_D = +6.5$ (c 0.1, $CHCl_3$); IR (neat, cm^{-1}): 1454.6, 1300.3, 1105.4, 754.1, 695.6 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.79 (d, 1H, J = 8.0 Hz, Aromatic), 7.44–7.08 (m, 17H, Aromatic), 5.13 (d, 1H, J = 4.4 Hz, H-1), 4.89–4.50 (m, 6H, CH_2Ph), 4.10–3.98 (m, 2H, H-3, H-7_a), 3.89–3.60 (m, 4H, H-4, H-5, H-6_a, H-6_b), 3.37 (bd, 1H, J = 3.0 Hz, H-7_b), 2.93–2.80 (m, 1H, H-2), 2.36 (s, 3H, PhCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.7, 138.1, 137.9, 137.6, 136.5, 133.9, 130.3, 128.6, 128.5, 128.4, 127.9, 127.8, 127.6, 123.7 (Aromatic), 78.0 (C-4), 77.3 (C-3), 74.3 (C-5), 74.1, 73.9, 73.4 (CH_2Ph), 69.3 (C-1), 68.4 (C-6), 49.4 (C-7), 39.5 (C-2), 21.6 (PhCH_3); HRMS (ESI): m/z $[M+Na]^+$ Calcd: 607.2131; Found: 607.2130.

(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-hexahydro-S-S-dioxothiochromeno[4,3-b]pyran (3c):

73% yield; white solid; mp 94–96°C; $[\alpha]_D = +21.5$ (c 0.1, $CHCl_3$); IR (neat, cm^{-1}): 454.3, 1300.1, 1149.9, 734.6, 695.3 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.56–7.08 (m, 18H, Aromatic), 5.15 (d, 1H, J = 4.8 Hz, H-1), 4.90 (d, 1H, J = 10.4 Hz, CH_AH$_B$Ph), 4.83 (d, 1H, J = 10.4 Hz, CH$_A$$H_B$Ph). 4.74 (d, 1H, J = 11.2 Hz, CH_AH$_B$Ph), 4.66 (d, 1H, J = 12.0 Hz, CH_AH$_B$Ph), 4.62–4.48 (m, 2H, the rest of the CH$_A$$H_B$Ph), 4.14–3.99 (m, 2H, H-3, H-7_a), 3.79–3.65 (m, 4H, H-4, H-5, H-6_a, H-6_b), 3.42 (dd, 1H, J = 3.2 Hz and 14.4 Hz, H-7_b), 2.85–2.70 (m, 4H,

H-2, PhCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 138.3, 137.8, 137.6, 137.4, 137.2, 134.4, 132.6, 132.3, 128.5, 128.4, 128.0, 127.8, 127.6, 125.9 (Aromatic), 78.9 (C-4), 74.6 (C-3), 74.2 (C-5, CH$_2$Ph), 73.8, 73.5 (CH$_2$Ph), 70.5 (C-1), 68.4 (C-6), 51.3 (C-7), 39.7 (C-2), 19.6 (PhCH$_3$); HRMS (ESI): m/z [M+NH_4^+]$^+$ Calcd: 602.2571; Found: 602.2577.

(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-tert-butyl-2,3,4,4a,5,10b-hexahydro-S,S-dioxothiochromeno[4,3-b] pyran (3d):

69% yield; white solid; 114–116°C; $[\alpha]_D$ = +44.0 (c 0.1, $CHCl_3$); IR (neat, cm^{-1}): 1455.0, 1299.2, 1105.2, 749.9, 695.7 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83 (d, 1H, J = 8.4 Hz, Aromatic), 7.65 (s, 1H, Aromatic), 7.52 (d, 1H, J = 8.0 Hz, Aromatic), 7.40–7.08 (m, 15H, Aromatic), 5.18 (d, 1H, J = 4.8 Hz, H-1), 4.88 (d, 1H, J = 10.8 Hz, CH_AH$_B$Ph), 4.81 (d, 1H, J = 10.8 Hz, CH$_A$$H_B$Ph), 4.72 (d, 1H, J = 11.2 Hz, CH_AH$_B$Ph), 4.64 (d, 1H, J = 12.0 Hz, CH_AH$_B$Ph), 4.57 (d, 1H, J = 12.0 Hz, CH$_A$$H_B$Ph), 4.51 (d, 1H, J = 11.2 Hz, CH$_A$$H_B$Ph), 4.05 (dd, 1H, J = 7.8 Hz and 9.4 Hz, H-3), 3.98 (dd, 1H, J = 5.8 Hz and 14.2 Hz, H-7$_a$), 3.83–3.56 (m, 4H, H-4, H-5, H-6$_a$, H-6$_b$), 3.41 (dd, 1H, J = 3.8 Hz and 14.2 Hz, H-7$_b$), 2.88–2.69 (m, 1H, H-2), 1.28 (s, 9H, Ph(CH_3)$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.8, 138.2, 137.8, 137.5, 136.5, 133.4, 128.5, 128.4, 128.0, 127.9, 127.7, 126.7, 125.0, 123.6 (Aromatic), 78.9 (C-4), 77.4 (C-3), 74.5 (C-5), 74.3, 74.1, 73.6 (CH$_2$Ph), 70.1 (C-1), 68.6 (C-6), 49.6 (C-7), 40.1 (C-2), 35.2 (PhC(CH$_3$)$_3$), 30.9 (PhC(CH$_3$)$_3$); HRMS (ESI): m/z [M+NH_4^+]$^+$ Calcd: 644.3040; Found: 644.3038.

(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methoxy-2,3,4,4a,5,10b-hexahydro-S-S-dioxothiochromeno[4,3-b]pyran (3e):

70% yield; white solid; 99–101°C; $[\alpha]_D$ = +39.5 (c 0.1, $CHCl_3$); IR (neat, cm^{-1}): 1600.5, 1299.5, 1290.4, 1089.5, 744.8, 696.1 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (d, 1H, J = 8.8 Hz, Aromatic), 7.50–7.04 (m, 16H, Aromatic), 7.00 (d, 1H, J = 9.2 Hz, Aromatic), 5.15 (d, 1H, J = 5.2 Hz, H-1), 4.91–4.70 (m, 3H, CH_2Ph), 4.66–4.49 (m, 3H, CH_2Ph), 4.07 (t, 1H, J = 8.8 Hz, H-3), 3.95 (dd, 1H, J = 5.2 Hz and 14.4 Hz, H-7$_a$), 3.88–3.57 (m, 7H, H-4, H-5, H-6$_a$, H-6$_b$, PhOCH_3), 3.42 (dd, 1H, J = 3.2 Hz and 14.4 Hz, H-7$_b$), 2.91–2.78 (m, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0, 138.2, 137.7, 137.6, 136.2, 131.3, 128.5, 128.4, 128.0, 127.8, 127.6, 125.8, 116.3, 111.6 (Aromatic), 79.1 (C-4), 77.4 (C-3), 74.6 (C-5), 74.3, 74.1, 73.6 (CH$_2$Ph), 70.2 (C-1), 68.7 (C-6), 55.5 (PhOCH$_3$), 49.6 (C-7), 40.2 (C-2); HRMS (ESI): m/z [M+H^+]$^+$ Calcd: 601.2261; Found: 601.2272.

General Procedure for the Synthesis of Sulfones 5a–e

A solution of sulfone **3a–e** (0.25 mmol) in DMF (1 mL) was added to a vigorously stirring suspension of sodium hydride (60% dispersion on oil, 15 mg,

0.38 mmol) in DMF (1 mL) and the mixture was stirred at rt. After 15 min stirring of the reaction mixture, water (10 mL) was added and the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvent in vacuo, the crude product was purified by flash chromatography on silica gel (ethyl acetate/hexane, 3:7) to give the corresponding epimerized sulfones **5a–e**.

(2R,3S,4R,4aS,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydro-S,S-dioxothiochromeno[4,3-b]pyran (5a):

87% yield; white solid; mp 98–100°C; $[\alpha]_D = +5.8$ (*c* 0.5, $CHCl_3$); IR (neat, cm^{-1}): 1304, 696; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.95–7.05 (m, 19H, Aromatic), 4.96 (d, $J = 11.2$ Hz, 1H, CH_AH$_B$Ph), 4.83 (d, $J = 10.8$ Hz, 1H, CH_AH$_B$Ph), 4.75–4.50 (m, 4H, the rest of the CH_2Ph), 4.38 (d, $J = 10.4$ Hz, 1H, H-1), 3.95–3.35 (m, 6H, H-6_a, H-6_b, H-4, H-5, H-7_a, H-3), 2.91 (t, $J = 13.0$ Hz, 1H, H-7_b), 2.78–2.55 (m, 1H, H-2); ^{13}C NMR: ($CDCl_3$, 100 MHz): δ 137.9, 137.7, 137.4, 137.4, 135.0, 132.6, 129.0, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.0, 123.3 (Aromatic), 82.0 (C-3), 79.8 (C-5), 79.2 (C-4), 75.1 (*C*H$_2$Ph), 75.0 (*C*H$_2$Ph), 75.0 (C-1), 73.5 (*C*H$_2$Ph), 68.8 (C-6), 50.8 (C-7), 42.2 (C-2); HRMS (ESI): *m*/*z* [M+NH_4^+]$^+$ Calcd: 588.2420; Found: 588.2427.

(2R,3S,4R,4aS,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methyl-2,3,4,4a,5,10b-hexahydro-S,S-dioxothiochromeno[4,3-b]pyran (5b):

88% yield; white solid; mp 94–96°C; $[\alpha]_D = +3.5$ (*c* 0.5, $CHCl_3$); IR (neat, cm^{-1}): 1304, 697; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, $J = 8.0$ Hz, 1H, Aromatic), 7.52 (s, 1H, Aromatic), 7.45–7.10 (m, 16H, Aromatic), 4.96 (d, $J = 11.2$ Hz, 1H, CH_AH$_B$Ph), 4.84 (d, $J = 10.8$ Hz, 1H, CH_AH$_B$Ph), 4.75–4.50 (m, 4H, the rest of the CH_2Ph), 4.35 (d, $J = 10.4$ Hz, 1H, H-1), 3.95–3.40 (m, 6H, H-6_a, H-6_b, H-4, H-5, H-7_a, H-3), 2.91 (t, $J = 12.8$ Hz, 1H, H-7_b), 2.75–2.55 (m, 1H, H-2), 2.40 (s, 3H, PhCH_3); ^{13}C NMR: ($CDCl_3$, 100 MHz): δ 143.4, 138.0, 137.7, 137.4, 134.9, 134.7, 129.7, 128.7, 128.5, 128.4, 128.2, 128.1, 127.9, 127.9,127.8, 127.7, 127.3, 123.4 (Aromatic), 82.1 (C-3), 79.8 (C-5), 79.3 (C-4), 75.1 (*C*H$_2$Ph), 75.1 (*C*H$_2$Ph), 75.0 (C-1), 73.4 (*C*H$_2$Ph), 68.7 (C-6), 50.8 (C-7), 42.3 (C-2), 21.7 (Ph*C*H$_3$); HRMS (ESI): *m*/*z* [M+NH_4^+]$^+$ Calcd: 602.2577; Found: 602.2569.

(2R,3S,4R,4aS,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-hexahydro-S-S-dioxothiochromeno[4,3-b]pyran (5c):

85% yield; white solid; mp 151–152°C; $[\alpha]_D = +4.5$ (*c* 0.5, $CHCl_3$); IR (neat, cm^{-1}): 1304, 699; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.60 (d, $J = 7.6$ Hz, 1H, Aromatic), 7.50–7.10 (m, 17H, Aromatic), 4.97 (d, $J = 11.2$ Hz, 1H, CH_AH$_B$Ph), 4.84 (d, $J = 10.8$ Hz, 1H, CH_AH$_B$Ph), 4.75–4.50 (m, 4H, the rest of the CH_2Ph), 4.30 (d, $J = 10.4$ Hz, 1H, H-1), 3.95–3.35 (m, 6H, H-6_a, H-6_b, H-4, H-5, H-7_a, H-3), 2.90 (t, $J = 13.2$ Hz, 1H, H-7_b), 2.80–2.50 (m, 4H, H-2, PhCH_3); ^{13}C NMR:

($CDCl_3$, 100 MHz): δ 138.0, 137.7, 137.5, 136.6, 135.7, 135.3, 132.3, 131.7, 128.7, 128.5, 128.4, 128.2, 128.2, 127.9, 127.9, 127.8, 127.7, 125.1 (Aromatic), 82.0 (C-3), 79.8 (C-5), 79.2 (C-4), 75.5 (CH_2Ph), 75.1 (CH_2Ph), 75.0 (C-1), 73.5 (CH_2Ph), 68.8 (C-6), 52.5 (C-7), 41.6 (C-2), 19.7 (PhCH_3); HRMS (ESI): m/z $[M+NH_4^+]^+$ Calcd: 602.2571; Found: 602.2583.

(2R,3S,4R,4aS,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-tert-butyl-2,3,4,4a,5,10b-hexahydro-S,S-dioxothiochromeno[4,3-b]pyran (5d):

94% yield; white solid; mp 159–161°C; $[\alpha]_D = +4.8$ (c 0.5, $CHCl_3$); IR (neat, cm^{-1}): 1301, 696; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.85–7.68 (m, 2H, Aromatic), 7.49 (d, J = 8.4 Hz, 1H, Aromatic), 7.45–7.15 (m, 15H, Aromatic), 4.96 (d, J = 11.6 Hz, 1H, CH_AH$_B$Ph), 4.85 (d, J = 11.2 Hz, 1H, CH_AH$_B$Ph), 4.75–4.50 (m, 4H, the rest of the CH_2Ph), 4.37 (d, J = 10.4 Hz, 1H, H-1), 3.95–3.40 (m, 6H, H-6$_a$, H-6$_b$, H-4, H-5, H-7$_a$, H-3), 2.90 (t, J = 13.2 Hz, 1H, H-7$_b$), 2.75–2.55 (m, 1H, H-2), 1.31 (s, 9H, PhC(CH_3)$_3$); ^{13}C NMR: ($CDCl_3$, 100 MHz): δ 156.3, 138.1, 137.7, 137.4, 134.6, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.7, 127.7, 126.3, 123.6, 123.2 (Aromatic), 82.2 (C-3), 79.9 (C-5), 79.4 (C-4), 75.2 (CH_2Ph), 75.1 (CH_2Ph), 75.0 (C-1), 73.6 (CH_2Ph), 68.9 (C-6), 50.8 (C-7), 42.4 (C-2), 35.3 (PhC(CH$_3$)$_3$), 31.0 (PhC(CH_3)$_3$); HRMS (ESI): m/z $[M+NH_4^+]^+$ Calcd: 644.3040; Found: 644.3049.

(2R,3S,4R,4aS,10bR)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-methoxy-2,3,4,4a,5,10b-hexahydro-S-S-dioxothiochromeno[4,3-b]pyran (5e):

92% yield; white solid; mp 132–134°C; $[\alpha]_D = +3.6$ (c 0.5, $CHCl_3$); IR (neat, cm^{-1}): 1321, 646; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, J = 8.4 Hz, 1H, Aromatic), 7.50–7.10 (m, 16H, Aromatic), 6.96 (d, J = 8.4 Hz, 1H, Aromatic), 4.96 (d, J = 11.2 Hz, 1H, CH_AH$_B$Ph), 4.75 (d, J = 10.8 Hz, 1H, CH_AH$_B$Ph), 4.75–4.50 (m, 4H, the rest of the CH_2Ph), 4.36 (d, J = 10.4 Hz, 1H, H-1), 3.95–3.40 (m, 9H, PhOCH_3, H-6$_a$, H-6$_b$, H-4, H-5, H-7$_a$, H-3), 2.90 (t, J = 12.8 Hz, 1H, H-7$_b$), 2.75–2.55 (m, 1H, H-2); ^{13}C NMR: ($CDCl_3$, 100 MHz): δ 162.8, 138.0, 137.7, 137.4, 137.4, 129.5, 128.7, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.7, 125.5, 114.9, 111.6 (Aromatic), 82.2 (C-3), 79.8 (C-5), 79.3 (C-4), 75.1 (CH_2Ph), 75.0 (CH_2Ph), 74.9 (C-1), 73.5 (CH_2Ph), 68.8 (C-6), 55.5 (PhOCH_3), 50.9 (C-7), 42.4 (C-2); HRMS (ESI): m/z $[M+NH_4^+]^+$ Calcd: 618.2526; Found: 618.2516.

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REFERENCES

1. (a) Yoneya, T.; Taniguchi, K.; Nakamura, R.; Tsunenari, T.; Ohizumi, I.; Kanbe, Y.; Morikawa, K.; Kaiho, S.-I.; Yamada-Okabe, H. Thiochroman derivative CH4986399, a

new nonsteroidal estrogen receptor down-regulator, is effective in breast cancer models. *Anticancer Res.* **2010**, *30*, 873–878. (b) Kanbe, Y.; Kim, M.-H.; Nishimoto, M.; Ohtake, Y.; Tsunenari, T.; Taniguchi, K.; Ohizumi, I.; Kaiho, S.-I.; Nabuchi, Y.; Kawata, S.; Morikawa, K.; Jo, J.-C.; Kwon, H.-A.; Lim, H.-S.; Kim, H.-Y. Discovery of thiochroman derivatives bearing a carboxy-containing side chain as orally active pure antiestrogens. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4090–4094.

2. Xia, P.; Yin, Z.-J., Chen, Y.; Zhang, Q.; Zhang, B.; Xia, Y.; Yang, Z.-Y.; Kilgore, N.; Wild, C.; Morris-Natschke, S.L.; Lee, K.-H. Anti-AIDS agents. Part 58: synthesis and anti-HIV activity of 1-thia-di-*O*-(-)-camphanoyl-(+)-*cis*-khellactone (1-thia-DCK) analogues. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3341–3343 and references cited therein.

3. Razdan, R.K.; Bruni, R.J.; Mehta, A.C.; Weinhardt, K.K.; Papanastassiou, Z.B. A new class of antimalarial drugs: derivatives of benzothiopyrans. *J. Med. Chem.* **1978**, *21*, 643–649.

4. Brown, M.J.; Carter, P.S.; Fenwick, A.E.; Fosberry, A.P.; Hamprecht, D.W.; Hibbs, M.J.; Jarvest, R.L.; Mensah, L.; Milner, P.H.; O'Hanlon, P.J.; Pope, A.J.; Richardson, C.M.; West, A.; Witty, D.R. The antimicrobial natural product chuangxinmycin and some synthetic analogues are potent and selective inhibitors of bacterial tryptophanyl tRNA synthetase. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3171–3174.

5. (a) Du, Z.; Zhou, C.; Gao, Y.; Ren, Q.; Zhang, K.; Cheng, H.; Wang, W.; Wang, J. Expeditious diastereoselective construction of a thiochroman skeleton via a cinchona alkaloid-derived catalyst. *Org. Biomol. Chem.* **2012**, *10*, 36–39 and references cited therein. (b) van Vliet, L.A.; Rodenhuis, N.; Dijkstra, D.; Wikström, H. Synthesis and pharmacological evaluation of thiopyran analogues of the dopamine D_3 receptor-selective agonist (4a*R*,10b*R*)-(+)-*trans*-3,4,4a,10b-tetrahydro-4-*n*-propyl-2*H*,5*H*-[1]benzopyrano[4,3-*b*]-1,4-oxazin-9-ol (PD 128907). *J. Med. Chem.* **2000**, *43*, 2871–2882.

6. (a) Bolognesi, M.L.; Bartolini, M.; Cavalli, A.; Andrisano, V.; Rosini, M.; Minarini, A.; Melchiorre, C. Design, synthesis, and biological evaluation of conformationally restricted rivastigmine analogues. *J. Med. Chem.* **2004**, *47*, 5945–5952. (b) Seifert, A.; Mahrwald, R. Stereoselective one-pot synthesis of highly differently substituted thiochromans. *Tetrahedron Lett.* **2009**, *50*, 6466–6468.

7. Spruce, L.W.; Rajadhyaksha, S.N.; Berlin, K.D.; Gale, J.B.; Miranda, E.T.; Ford, W.T.; Blossey, E.C.; Verma, A.K.; Hossain, M.B.; Helm, D.V.D.; Breitman, T.R. Heteroarotinoids. synthesis, characterization, and biological activity in terms of an assessment of these systems to inhibit the induction of ornithine decarboxylase activity and to induce terminal differentiation of HL-60 Cells. *J. Med. Chem.* **1987**, *30*, 1474–1482.

8. Jafarzadeh, M.; Amani, K.; Nikpour, F. Solvent-free and room temperature synthesis of thiochromans in the presence of a catalytic amount of tungstophosphoric acid. *Tetrahedron Lett.* **2005**, *46*, 7567–7569.

9. Cossy, J.; Leblanc, H.C. A very short access to 4-substituted thiochromanes. *Tetrahedron Lett.* **1987**, *28*, 1417–1418.

10. Labiad, B.; Villemin, D. Clay catalysis: synthesis of organosulphur synthons. *Synth. Commun.* **1989**, *19*, 31–38.

11. Ishino, Y.; Mihara, M.; Kawai, H. Improved method for synthesis of 4-thioaryl-2,3,4-trihydro-1-benzothiopyrans: acid-induced stereoselective intermolecular cycloaddition of a,b-unsaturated aldehydes with arenethiols. *Synlett*. **2001**, *8*, 1317–1319.

12. Aoyama, T.; Okada, K.; Nakajima, H.; Matsumoto, T.; Takido, T.; Kodomari, M. Stereoselective synthesis of 2,4-disubstituted thiochromans using the supported reagent system Na_2CO_3/SiO_2-PPA/SiO_2. *Synlett*. **2007**, 3, 387–390.

13. Evans, D.A.; Michael, F.E.; Tedrow, J.S.; Campos, K.R. Application of chiral mixed phosphorus/sulfur ligands to enantioselective rhodium-catalyzed dehydroamino acid hydrogenation and ketone hydrosilylation processes. *J. Am. Chem. Soc.*, **2003**, *125*, 3534–3543.

14. Zhang, X.; Taketomi, T.; Yoshizumi, T.; Kumobayashi, H.; Akutagawa, S.; Mashima, K.; Takaya, H. Asymmetric hydrogenation of cycloalkanones catalyzed by BINAP-iridium(I)-aminophosphine systems. *J. Am. Chem. Soc.* **1993**, *115*, 3318–3319.

15. Zhang, B.; Xiang, S.-K.; Zhang, L.-H.; Cui, Y.; Jiao, N. Organocatalytic asymmetric intermolecular dehydrogenative α-alkylation of aldehydes using molecular oxygen as oxidant. *Org. Lett.* **2011**, *13*, 5212–5215.

16. Dodda, R.; Mandal, T.; Zhao, C.-G. Organocatalytic highly enantioselective tandem Michael–Knoevenagel reaction for the synthesis of substituted thiochromanes. *Tetrahedron Lett.* **2008**, *49*, 1899–1902 and references cited therein.

17. (a) Zu, L.; Wang, J.; Li, H.; Xie, H.; Jiang, W.; Wang, W. Cascade Michael−aldol reactions promoted by hydrogen bonding mediated catalysis. *J. Am. Chem. Soc.* **2007**, *129*, 1036–1037. (b) Fukamizu, K.; Miyake, Y.; Nishibayashi, Y. Ruthenium-catalyzed enantioselective carbon-carbon bond forming reaction via allenylidene-ene process: synthetic approach to chiral heterocycles such as chromane, thiochromane, and 1,2,3,4-tetrahydroquinoline derivatives. *J. Am. Chem. Soc.* **2008**, *130*, 10498–10499.

18. Dodda, R.; Goldman, J.J.; Mandal, T.; Zhao, C.-G.; Broker, G.A.; Tiekink, E.R.T. Synthesis of 2,3,4-trisubstituted thiochromanes using an organocatalytic enantioselective tandem Michael-Henry reaction. *Adv. Synth. Catal.* **2008**, *350*, 537–541.

19. (a) Wang, J.; Xie, H.-X.; Li, H.; Zu, L.-S.; Wang, W. Hydrogen-bond mediated highly stereoselective cascade Michael-Michael process via dynamic kinetic resolution. *Angew. Chem. Int. Ed.* **2008**, *47*, 4177–4179. (b) Saito, T.; Horikoshi, T.; Otani, T.; Matsuda, Y.; Karakasab, T. A facile and efficient one-pot synthesis of thiochromans from bis(2-formylphenyl) disulfide and alkenols *via* iodine-promoted generation and subsequent intramolecular cycloaddition of *ortho*-thiobenzoquinone methides. *Tetrahedron Lett.* **2003**, *44*, 6513–6517. (c) Inoue, S.; Wanga, P.; Nagaoa, M.; Hoshinoa, Y.; Honda, K. One-pot stereoselective synthesis of pyrano[3,2-c]benzothiopyrans: a new generation and [4+2] cycloaddition of *ortho*-thioquinonemethides. *Synlett*. **2005**, 469–472.

20. Kinfe, H.H.; Moshapo, P.T.; Makolo, F.L.; Muller, A. Facile diastereoselective synthesis of carbohydrate based thiochromans. *J. Carbohydr. Chem.* **2013**, *32*, 139–157.

21. Kurth, M.J.; O'Brien, M.J. Desulfurization/α-alkylation of β-keto sulfones. *J. Org. Chem.* **1985**, *50*, 3846–3848.

22. (a) Lindhorst, T.K. *Essentials of Carbohydrate Chemistry and Biochemistry, 3rd ed*. Wiley-VCH: Weinheim, **2007**. (b) Osborn, H.M.I. *Carbohydrates*. Academic Press: Oxford, **2003**.

23. Refer to the supplementary information for full crystalographic data.

24. For the synthesis of thiochromans **1a–e** refer to reference 20.