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Stereoselective Synthesis of Thiochromenes via Intramolecular Tandem Thio-Michael Addition of in Situ Generated α,β-Unsaturated Aldehydes

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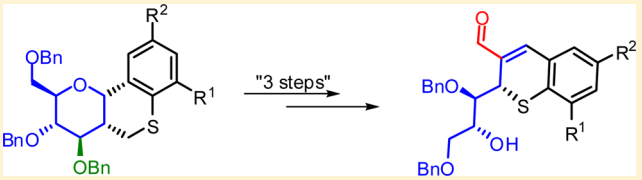
Supporting Information

ABSTRACT: An efficient and highly stereoselective strategy for the synthesis of 2,3-substituted thiochromenes having a complex and easily transformable group at the stereogenic center has been developed via a tandem thio-Michael addition reaction of an in situ generated α,β-unsaturated aldehyde sugar derivative. The protocol is superior to reported protocols in that the carbohydrate-derived substituent at the stereogenic center of the thiochromene is versatile and is amenable for further transformation.



INTRODUCTION

2*H*-1-Benzothiopyrans **1**, commonly known as thiochromenes, are an important heterocyclic class of compounds found in a number of pharmaceutical agents[1−5] including anticancer,[6,7] anticonvulsant,[8] anti-HIV,[9] and antibacterial agents.[7] Owing to their pharmacological importance, a number of synthetic protocols have been reported for the synthesis of thiochromenes.[10−15] However, there have been very few literature reports on stereoselective synthetic approaches to such compounds. Kobayashi and co-workers reported on the synthesis of thiochromenes in 92−93% ee via condensation of 2-mercaptobenzophenone and α,β-unsaturated carboxylates in the presence of (diisopropylamino)magnesium reagent followed by dehydration.[16] Córdova et al. and Wang et al. have independently reported on a highly stereoselective (91−98% ee) chiral pyrrolidine catalyzed domino thia-Michael/aldol reaction of 2-mercaptobenzaldehydes and α,β-unsaturated aldehydes for the synthesis of thiochromene derivatives.[17−19] Although these methods are efficient, they are limited to providing chiral thiochromenes with simple *n*-alkyl or phenyl substituents at the C-2 stereogenic center. As a result of this limitation, the search for the development of stereoselective synthetic protocols, which can provide thiochromenes having versatile substituents and are amenable for further functionalization at the stereogenic center, are crucial. We recently reported on the stereoselective synthesis of carbohydrate-based thiochroman **3** via Lewis acid catalyzed intramolecular Friedel−Crafts alkylation whereby the stereochemistry at the C-2 position of the sugar moiety determines the stereochemical outcome of the product (Scheme 1).[20] As an extension of this early report, we now wish to report a highly diastereoselective synthesis of a series of novel 2,3-substituted chromene-3-carbaldehydes **4** (Figure 1) via intramolecular tandem Michael addition-type reaction of an in situ generated α,β-unsaturated aldehyde making use of thiochroman **3** as a camouflaged hemithioacetal and as is illustrated in Scheme 2.

RESULT AND DISCUSSION

To determine the optimal reaction conditions, thiochroman **3a** was used as a model substrate. Thus, it was oxidized with cerium ammonium nitrate to provide the sulfoxide **5a** as a diastereomeric mixture in 68% combined yield. Pummerer rearrangement of the diastereomeric mixture of sulfoxides **5a** with NaOAc in acetic anhydride under refluxing conditions[21,22] followed by suspension of the crude product in a 1:1 mixture of methanol and dichloromethane in the presence of a catalytic amount of NaOMe at room temperature for 10 min afforded thiochromene **4a** in 80% yield over two steps (Scheme 2). Similar results were obtained when other milder bases such as $NaHCO_3$, $KHCO_3$, and K_2CO_3 were employed. The substituent at C-2 of the thiochromene was the open sugar chain moiety with its stereochemistry intact.

The structure of thiochromene **4a** was established using NMR spectroscopy and HRMS. The appearance of the aldehydic proton signal at δ_H 9.51 and carbon signal at δ_C 193.6 confirmed the presence of an aldehyde functional group. The appearance of H-2 as a doublet at δ_H 4.39 due to coupling to H-1′ only and the C-4 and H-4 signals downfield in the aromatic region (as evidenced from HMBCAD spectrum due to coupling to the aldehydic proton) suggested the presence of a double bond between C-3 and C-4. To confirm the presence and position of the OH group, thiochromene **4a** was transformed into the acetylated product **6a** in quantitative yield (Scheme 2). The downfield shift of H-2′ from around δ_H 3.50 in thiochromene **4a** to the region of δ_H 5.20−5.03 in thiochromene **6a** coupled with

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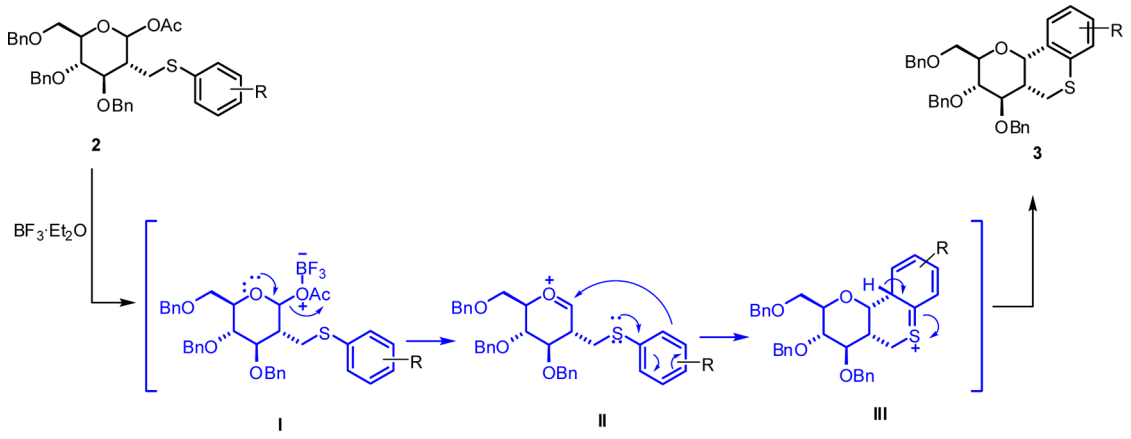
Scheme 1. Proposed Mechanism for the Formation of the Carbohydrate-Based Thiochroman 3[20]



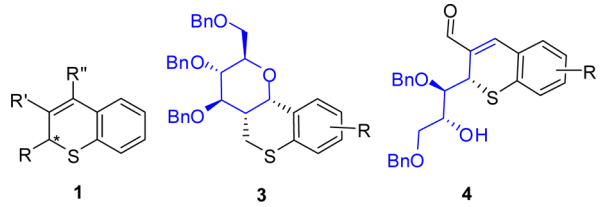
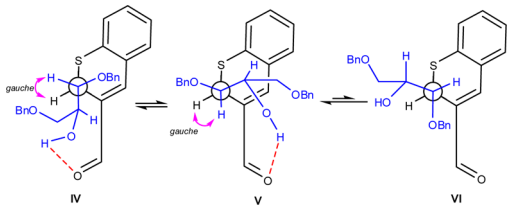


Figure 1. General structure of thiochromene **1**, carbohydrate-based thiochroman **3**, and chromene-3-carbaldehyde derivatives **4**.

Scheme 3. Possible Staggered Conformations of Thiochromene 4a



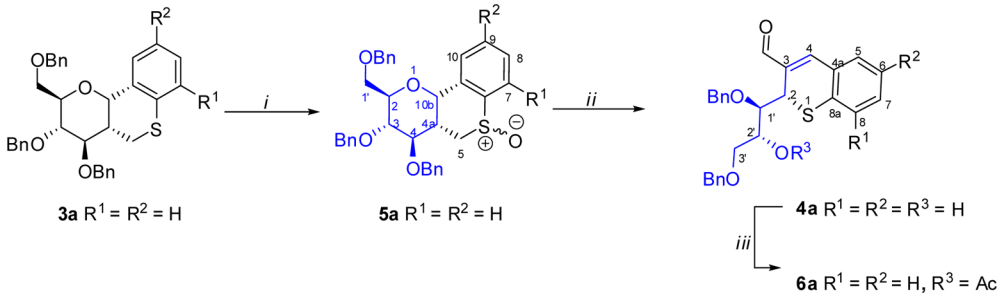
the appearance of the OAc signals at δ_H 2.06, δ_C 169.9 and 21.1 confirmed acetylation of the OH group at C-2′ (C-2′ in **6a** corresponds to C-2 in **5a**), which indirectly indicated an opening of the sugar ring. Moreover, the integration of the methylene signals of the benzyl protecting groups was found to be four, confirming the cleavage of one benzyl group from the starting thiochroman.

The *S*-configuration at the C-2 stereogenic center was determined by measuring the $^3J_{H\text{-}2,H\text{-}1'}$ coupling constant. The $^3J_{H\text{-}2,H\text{-}1'}$ coupling constant was found to be 3.4 Hz for thiochromene **4a** and corresponds to a *gauche* relationship between the H-2 and H-1′ protons.[23] In the *S*-configuration at C-2, thiochromene **4a** would possibly adopt two favored staggered conformations (**IV** and **V**) due to hydrogen bonding and a less favored conformation **VI** (Scheme 3) having a *gauche* and *anti* relationship between the H-2 and H-1′ protons, respectively. Hence, a smaller $^3J_{H\text{-}2,H\text{-}1'}$ coupling constant was observed. Had the configuration at C-2 been *R*, thiochromene **4a** would have adopted a conformation having *anti* relationship between H-2 and H-1′ as one of its preferred conformers, and this would have resulted in a larger $^3J_{H\text{-}2,\ H\text{-}1'}$ coupling constant. In thiochromene **6a**, the absence of the hydrogen-bonding stabilization in the staggered conformations was confirmed from the relatively higher $^3J_{H\text{-}2,\ H\text{-}1'}$ coupling constant (5.7 Hz inferred from the signal of H-1′) which resulted from the average of all the possible conformers.

With the optimized reaction conditions in hand, the scope of this diastereoselective thiochromene synthesis with various thiochroman **3** derivatives was examined. Following the developed protocol, several thiochromans **3a**−**e** were transformed stereoselectively to thiochromene-3-carbaldehydes **6a**−**e**, and the results are summarized in Table 1.

The proposed mechanism is illustrated in Scheme 4. The sulfoxide is transformed into the acetate **7** via Pummerer rearrangement. Hydrolysis of the acetate results in formation of the hemimercaptal derivative **8** which equilibrates with the mercaptoaldehyde **9**.[24] Deprotonation of the acidic α-hydrogen gives an enolate **10**, which then undergoes cleavage of the benzyloxy under the alkaline conditions to provide the α,β-unsaturated

Scheme 2[a]



[a]Key: (i) CAN, wet silica, KBr, CH_2Cl_2/CH_3CN (1:1), rt, 30 min, 68%; (ii) (a) NaOAc, Ac_2O, 140 °C, 3 h; (b) NaOMe, CH_2Cl_2/CH_3OH (1:1), rt, 10 min, 80%; (iii) Ac_2O, Et_3N, DMAP, rt, 30 min, 79%.

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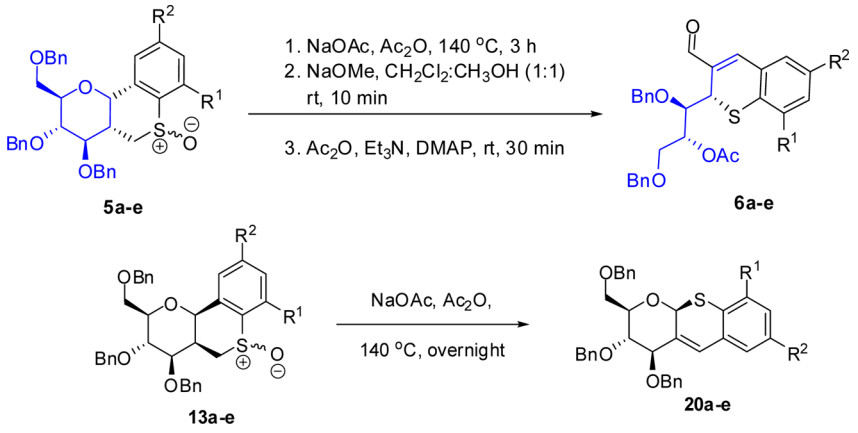
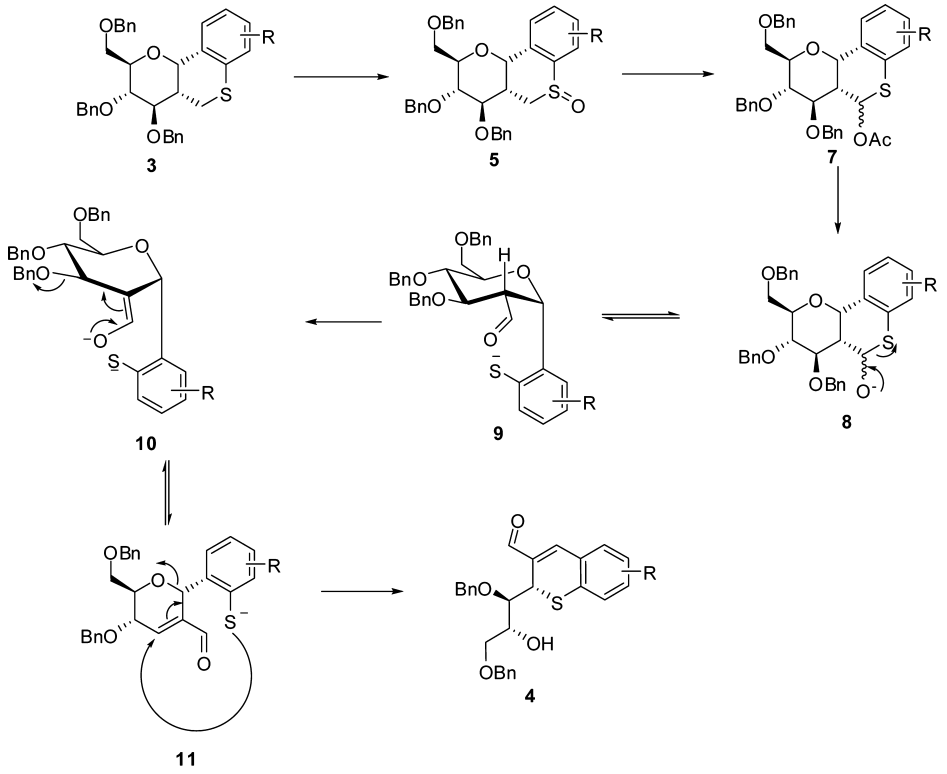
Table 1. Formation of Thiochromenes 6a−e and 20a−e Using Sulfoxides 5a−e and 13a−e



entry	sulfoxide substrate (diastereomeric ratio)	thiochromene product	isolated yield (%)
1	**5a** $R^1 = R^2 = H$ (1:1.5)	**6a** $R^1 = R^2 = H$	79
2	**5b** $R^1 = H$, $R^2 = CH_3$ (1:1.8)	**6b** $R^1 = H$, $R^2 = CH_3$	69
3	**5c** $R^1 = H$, $R^2 = OCH_3$ (1:2)	**6c** $R^1 = H$, $R^2 = OCH_3$	69
4	**5d** $R^1 = H$, $R^2 = C(CH_3)_3$ (1:1.2)	**6d** $R^1 = H$, $R^2 = C(CH_3)_3$	75
5	**5e** $R^1 = CH_3$, $R^2 = H$ (1:1.5)	**6e** $R^1 = CH_3$, $R^2 = H$	72
6	**13a** $R^1 = R^2 = H$ (1:2.3)	**20a** $R^1 = R^2 = H$	63
7	**13b** $R^1 = H$, $R^2 = CH_3$ (1:2.3)	**20b** $R^1 = H$, $R^2 = CH_3$	86
8	**13c** $R^1 = H$, $R^2 = OCH_3$	**20c** $R^1 = H$, $R^2 = OCH_3$	60
9	**13d** $R^1 = H$, $R^2 = C(CH_3)_3$ (1:2.6)	**20d** $R^1 = H$, $R^2 = C(CH_3)_3$	66
10	**13e** $R^1 = CH_3$, $R^2 = H$ (1:2)	**20e** $R^1 = CH_3$, $R^2 = H$	85

Scheme 4. Proposed Mechanism of the One-Pot Tandem Michael Addition-Type Reaction for the Stereoselective Synthesis of Thiochromene 4



aldehyde **11** in accordance with the literature report by Yamakawa et al.[25] Attack by the thiolate at the β-position of the double bond provides the desired thiochromene **4** via tandem Michael addition-type reaction.

Selectivity in favor of the *S*-configuration at the C-2 position of thiochromenes **4** could be explained in terms of the preference in the α,β-unsaturated aldehyde intermediate **11** for the $^{O}H_{S}$ conformation (Figure 2).[26] In this conformation, the thiolate

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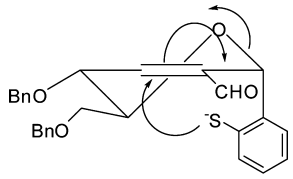


Figure 2. Preferred $^{O}H_{5}$ conformation of α,β-unsaturated aldehyde intermediate **11**.

moiety is prepositioned for intramolecular delivery from the α-face of the sugar unit to give the stereochemistry depicted in thiochromene **4**.

After the successful stereoselective synthesis of thiochromenes **6a–e**, we envisioned the potential synthesis of thiochromene **16** (with opposite stereochemistry at C-2 to that of **4**) using the same reaction sequences but starting with thiochroman **12** as proposed in Scheme 5. However, treatment of the sulfoxide **13** under Pummerer reaction conditions failed to provide the hemithioacetal derivative **15** via acetate attack at the α-carbon of the sulfonium intermediate **14**. Instead, the reaction provided thiochromene **20** (entries 6–10 in Table 1) presumably by abstraction of the β-hydrogen of the sulfonium intermediate **17** by the acetate ion followed by rearrangement of the aryl-*C*-glycoside **18** to the corresponding aryl *S*-glycoside **20** as shown in Scheme 5. The possibility of this rearrangement occurring during workup and isolation cannot be excluded. The abstraction of the β-hydrogen might have been favored by the possible coplanar arrangement of the H–C and C=S bonds in a similar fashion to an E2 elimination reaction. The structure of thiochromene **20** was determined using single-crystal X-ray crystallography.[27]

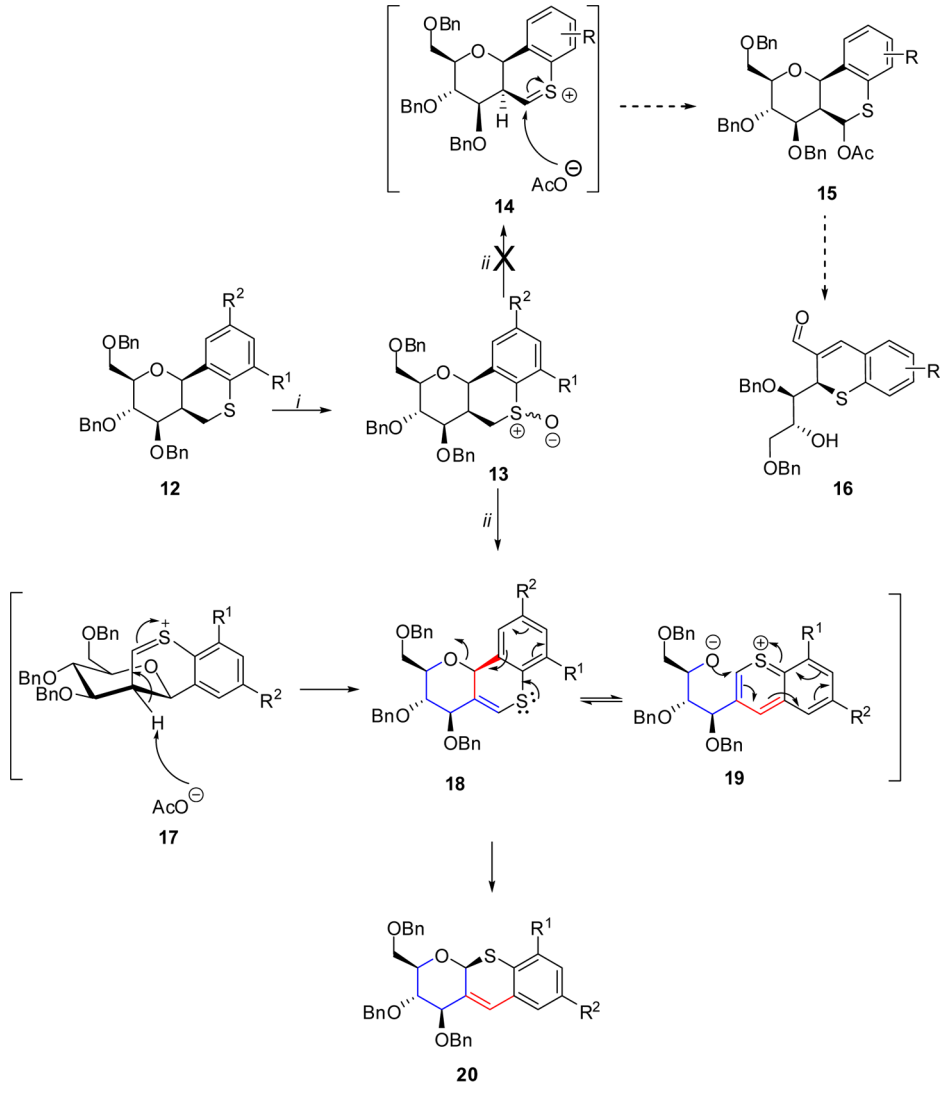
CONCLUSION

In conclusion, we have shown an efficient and highly stereoselective strategy for the synthesis of 2,3-substituted thiochromenes via a tandem thio-Michael addition reaction. The current protocol is superior to reported protocols in that the carbohydrate-derived substituent at the stereogenic center of the thiochromene is versatile and is amenable for further transformation. Application of this methodology for the synthesis of biologically important molecules is under way.

EXPERIMENTAL SECTION

General Methods. All of the solvents used were freshly distilled. Dichloromethane was distilled over phosphorus pentoxide in a

Scheme 5[a]



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condenser fitted with a drying tube containing calcium chloride. Other solvents were dried by appropriate techniques reported in *Purification of Laboratory Chemicals*.[28] Thiochromans **3a−e** and **12a−e** were synthesized according to previously published protocols.[20] All reactions were monitored by thin-layer chromatography (TLC) on an aluminum-backed 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% performed on silica gel 60 (70−230 mesh). Melting points were determined using a hot-stage apparatus and are uncorrected. Optical rotations were determined in chloroform solutions at 25 °C. The concentration *c* refers to g/100 mL. All proton and carbon-13 nuclear magnetic resonance spectra were recorded as deuteriochloroform solutions using tetramethylsilane as an internal standard. All chemical shifts are reported in ppm.

General Procedure for the Synthesis of Thiochroman Sulfoxide Derivatives 5a−e. KBr (0.15 mmol), 0.5 g of wet silica (50% w/w), and CAN (0.6 mmol) were consecutively added to the stirring solution of sulfides (**3a−e**) (0.5 mmol) dissolved in a 1:1 solution of CH_2Cl_2/CH_3CN (10 mL). The reaction was stirred for 30 min, and the solids were filtered through a pad of Celite. The solvents were removed under reduced pressure, and the diastereomeric mixture of sulfoxides was separated by column chromatography on silica gel using hexane and ethyl acetate as eluent (1:1) to afford sulfoxides **5a−e**.

*(2R,3S,4R,4aS,10bS)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**5a**, first diastereomer):* 110.9 mg, 40% yield; white solid; mp 103−105 °C; IR (neat cm^{-1}) 1454, 1090, 1025, 734, 695; $[\alpha]_D$ (*c* 0.1, $CHCl_3$) +84.0; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.84 (d, *J* = 7.2 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.60−7.44 (m, 2H), 7.42−7.07 (15H), 5.04 (d, *J* = 5.6 Hz, 1H), 4.96 (d, *J* = 10.4 Hz, 1H), 4.85−4.72 (m, 2H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.61−4.48 (m, 2H), 4.21 (dd, *J* = 7.6 and 10.0 Hz, 1H), 3.82−3.60 (m, 5H), 3.09 (dd, *J* = 3.8 and 14.6 Hz, 1H), 2.72−2.60 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 139.5, 138.8, 138.0, 133.5, 132.0, 129.1, 128.4, 128.0, 127.7, 127.6, 127.5, 79.4, 78.9, 74.2, 73.9, 73.5, 71.2, 68.8, 44.8, 35.8; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{35}O_5S$ 555.2205, found 555.2207.

*(2R,3S,4R,4aS,10bS)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**5a**, second diastereomer):* 74.9 mg, 27% yield; white solid; mp 68−70 °C; IR (neat cm^{-1}) 1454, 1049, 1024, 730, 696; $[\alpha]_D$ (*c* 0.1, $CHCl_3$) −4.0; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.2 Hz, 1H), 7.58−7.43 (m, 3H), 7.40−7.12 (m, 15H), 5.17 (d, *J* = 4.4 Hz, 1H), 4.79−4.50 (m, 6H), 3.94−3.84 (m, 2H), 3.82−3.71 (m, 2H), 3.70−3.58 (m, 2H,), 3.06−2.96 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 137.8, 137.7, 137.6, 134.2, 131.9, 130.0, 129.7, 129.3, 128.5, 128.4, 128.0, 127.8, 127.7, 127.6, 78.2, 76.6, 74.1, 74.0, 73.5, 73.4, 68.8, 68.0, 46.7, 34.9; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{34}H_{35}O_5S$ 555.2205, found 555.2207.

*(2R,3S,4R,4aS,10bS)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-9-methyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**5b**, first diastereomer):* 135.1 mg, 44% yield; white solid; mp 103−105 °C; IR (neat cm^{-1}) 1077, 1049, 740, 695; $[\alpha]_D$ (*c* 0.1, $CHCl_3$) −9.0; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.0 Hz, 1H), 7.53 (s, 1H), 7.41−7.10 (m, 16H), 5.04−4.97 (m, 2H), 4.78 (d, *J* = 10.8 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.61−4.50 (m, 2H), 4.26 (t, *J* = 9.2 Hz, 1H), 3.81−3.59 (m, 5H), 3.04 (dd, *J* = 3.6 and 14.8 Hz, 1H), 2.70−2.59 (m, 1H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.7, 138.8, 138.0, 136.3, 133.2, 131.2, 129.9, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 79.6, 78.8, 74.2, 73.8, 73.4, 71.4, 67.0, 44.6, 35.9, 21.6; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{35}H_{37}O_5S$ 569.2362, found 569.2354.

*(2R,3S,4R,4aS,10bS)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-9-methyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**5b** ,second diastereomer):* 73.7 mg, 24% yield; white solid; mp 104−106 °C; IR (neat cm^{-1}) 1454, 1049, 1026, 731, 696; $[\alpha]_D$ (*c* 0.1, $CHCl_3$) −11.5; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.42−7.13 (m, 15H), 5.11 (bs, 1H), 4.78−4.50 (m, 6H), 4.00−3.73 (m, 4H), 3.69−3.59 (m, 2H), 3.10−2.95 (m, 2H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 142.6, 137.9, 137.7, 137.6, 134.0, 130.4, 130.2, 130.1, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 78.2, 76.2, 74.1, 73.8, 73.3, 68.2, 68.0, 46.4, 33.9, 21.4; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{35}H_{37}O_5S$ 569.2362, found 569.2363.

*(2R,3S,4R,4aS,10bS)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-9-methoxy-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**5c**, first diastereomer):* 154.7 mg, 49% yield; white solid; mp 106−108 °C; IR (neat cm^{-1}) 1596, 1071, 1022, 735, 697; $[\alpha]_D$ (*c* 0.1, $CHCl_3$) −1.0; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 1H), 7.48−7.10 (m, 16H), 7.00 (d, *J* = 8.4 Hz, 1H), 5.11−4.99 (m, 2H), 4.80 (d, *J* = 10.4 Hz, 1H), 4.67−4.50 (m, 3H), 4.37 (t, *J* = 9.8 Hz, 1H), 3.85−3.62 (m, 7H), 3.61−3.50 (m, 1H), 2.99 (dd, 1H, *J* = 3.2 and 14.8 Hz), 2.73−2.61 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.8, 139.0, 138.0, 137.9, 134.5, 133.6, 130.6, 128.4, 128.3, 128.0, 128.0, 127.7, 127.6, 127.5, 127.4, 115.8, 111.4, 80.3, 78.6, 74.4, 74.3, 73.8, 73.6, 72.1, 69.3, 55.4, 44.1, 36.1; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{35}H_{37}O_6S$ 585.2311, found 585.2302.

*(2R,3S,4R,4aS,10bS)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-9-methoxy-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**5c**, second diastereomer):* 75.8 mg, 23% yield; colorless oil; IR (neat cm^{-1}) 1594, 1083, 1018, 738, 697; $[\alpha]_D$ (*c* 0.1, $CHCl_3$) +91.5; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 1H), 7.50−7.12 (m, 15H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.97 (dd, *J* = 2.4 and 8.8 Hz, 1H), 5.14 (d, *J* = 4.0 Hz, 1H), 4.80−4.50 (m, 6H), 3.93−3.70 (m, 7H), 3.65−3.52 (m, 2H), 3.06−2.92 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.4, 137.9, 137.7, 137.6, 136.3, 132.0, 128.6, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 115.8, 114.0, 78.5, 77.0, 74.2, 74.0, 73.5, 73.4, 68.8, 68.3, 55.5, 46.8, 34.7; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{35}H_{37}O_6S$ 585.2311, found 585.2308.

*(2R,3S,4R,4aS,10bS)-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-9-tert-butyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**5d**, first diastereomer):* 128.6 mg, 39% yield; white solid; mp 113−115 °C; IR (neat cm^{-1}) 1453, 1064, 735, 696; $[\alpha]_D$ (*c* 0.1, $CHCl_3$) −0.5; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.40 (dd, *J* = 1.6 and 8.4 Hz, 1H), 7.35−7.08 (m, 13H), 7.05−6.95 (m, 2H), 5.00−4.88 (m, 2H), 4.78−4.63 (m, 2H), 4.54 (d, *J* = 12.0 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.38 (d, *J* = 11.2 Hz, 1H), 4.20 (dd, *J* = 8.4 and 10.8 Hz, 1H), 3.70−3.40 (m, 5H), 2.92 (dd, *J* = 3.8 and 15.0 Hz, 1H), 2.65−2.50 (m, 1H); 1.19 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.0, 138.9, 137.8, 135.8, 132.2, 131.4, 128.0, 127.7, 127.6, 127.5, 126.3, 124.3, 80.2, 78.6, 74.5, 74.3, 73.7, 73.6, 72.0, 69.0, 44.2, 36.1, 35.1, 31.0; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{38}H_{43}O_5S$ 611.2831, found 611.2821.

*(2R,3S,4R,4aS,10bS)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-9-tert-butyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**5d**, second diastereomer):* 108.8 mg, 33% yield; white solid; mp 115−117 °C; IR (neat cm^{-1}) 1455, 1085, 1039, 749, 695; $[\alpha]_D$ (*c* 0.1, $CHCl_3$) +72.5; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 1H), 7.59 (s, 1H), 7.48 (dd, *J* = 1.6 and 8.0 Hz, 1H), 7.41−7.10 (m, 15H), 5.19 (d, *J* = 4.4 Hz, 1H), 4.80−4.49 (m, 6H), 3.95−3.85 (m, 2H), 3.80−3.70 (m, 2H), 3.65−3.57 (m, 2H), 3.04−2.94 (m, 2H), 1.28 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.6, 138.0, 137.8, 137.6, 136.4, 133.7, 129.9, 128.6, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 126.6, 126.5, 78.5, 77.0, 74.1, 73.7, 73.5, 69.2, 68.4, 46.9, 35.4, 35.0, 31.0; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{38}H_{43}O_5S$ 611.2831, found 611.2835.

*(2R,3S,4R,4aS,10bS)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**5e**, first diastereomer):* 132.1 mg, 43% yield; white solid; mp 99−101 °C; IR (neat cm^{-1}) 1594, 1070, 736, 697; $[\alpha]_D$ (*c* 0.1, $CHCl_3$) +38.5; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.6 Hz, 1H), 7.48−7.09 (m, 17H), 5.11 (d, *J* = 10.8 Hz, 1H), 5.05 (d, *J* = 5.6 Hz, 1H), 4.83 (d, *J* = 11.2 Hz, 1H), 4.67 (d, *J* = 12.0 Hz, 2H), 4.60−4.47 (m, 3H), 3.84 (dd, *J* = 3.2 and 15.2 Hz, 1H), 3.80−3.50 (m, 4H), 2.94 (dd, *J* = 3.0 and 15.0 Hz, 1H), 2.80−2.14 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.4, 139.1, 138.1, 137.9, 136.5, 133.8, 132.1, 131.2, 128.4, 128.3, 128.1, 127.8, 127.7, 127.5, 127.4, 127.3, 124.9, 80.6, 78.3, 74.4, 74.3, 73.5, 73.4, 72.9, 68.8, 43.0, 35.3, 19.4; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{35}H_{37}O_5S$ 569.2362, found 569.2362.

*(2R,3S,4R,4aS,10bS)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**5e** second diastereomer):* 86.0 mg, 28% yield; colorless oil; IR (neat cm^{-1}) 1453, 1089, 1028, 730, 695; $[\alpha]_D$ (*c* 0.1, $CHCl_3$) −24.0; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.6 Hz, 1H), 7.50−7.06 (17H), 5.10 (d, *J* = 10.4 Hz, 1H), 5.04 (d, *J* = 6.0 Hz, 1H), 4.87−4.76 (m, 2H), 4.66

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(d, J = 12.0 Hz, 1H), 4.58−4.45 (m, 3H), 3.84 (dd, J = 3.6 and 15.2 Hz, 1H), 3.75−3.68 (m, 2H), 3.72 (t, J = 2.0 Hz, 1H), 3.58−3.50 (m, 1H), 2.94 (dd, J = 3.8 and 15.0 Hz, 1H), 2.85−2.60 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.4, 139.2, 138.2, 138.0, 133.9, 132.2, 131.2, 128.4, 128.3, 128.1, 127.8, 127.7, 127.5, 127.4, 127.3, 124.9, 80.7, 78.3, 74.4, 74.3, 73.5, 72.9, 68.9, 43.1, 35.3, 19.4; HRMS (ES+-TOF) m/z $[M + H]^+$ calcd for $C_{35}H_{37}O_5S$ 569.2362, found 569.2364.

*(S)-2-((1R,2R)-1,3-Bis(benzyloxy)-2-hydroxypropyl)-2H-thiochromene-3-carbaldehyde (**4a**).* A stirred mixture of sulfoxide **5a** (160 mg, 0.29 mmol) and sodium acetate (4.1 mg, 0. 05 mmol) in acetic anhydride (1 mL) was refluxed at 140 °C for 3 h. The reaction was allowed to cool to room temperature. Diethyl ether (5 mL) and methanol (1 mL) were added to the reaction mixture and stirred for 1 h. The solution was concentrated at reduced pressure. The residue was diluted with dichloromethane and washed several times with saturated aqueous sodium bicarbonate solution. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give orange oil. To a solution of this oil in CH_2Cl_2 and CH_3OH (5 mL, 1:1) was added a catalytic amount of sodium methoxide, and the mixture was stirred at room temperature for 10 min. Water was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried, concentrated in vacuo, and flash chromatographed on silica gel (ethyl acetate/hexane, 1:9) to obtain thiochromene **4a** as a yellow syrup: 119.7 mg, 80% yield; $[\alpha]_D$ (c 0.1, $CHCl_3$) +26.5; IR (neat cm^{-1}) 3446, 1656, 1622, 1453, 1362, 1206, 1143, 1070, 732, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H, CHO), 7.38−6.90 (m, 13H, Ar and H-4), 6.44−6.56 (m, 2H, 2H, Ar), 4.34 (d, J = 10.6 Hz, 1H, CH_ACH_BPh), 4.28 (d, J = 10.6 Hz, 1H, CH_ACH_BPh), 4.39 (d, J = 3.6 Hz, 1H, H-2), 4.50 (d, J = 12.0 Hz, 1H, CH_ACH_BPh), 4.44 (d, J = 12.0 Hz, 1H, CH_ACH_BPh), 3.73 (dd, J = 3.2 and 8.4 Hz, 1H, H-1′), 3.61 (bd, J = 4.4 Hz, 1 H, OH), 3.60−3.35 (m, 3H, H-2′, H-3′$_a$, and H-3′$_b$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 193.6 (CHO), 149.7, 138.0, 137.4, 135.7, 131.7, 131.3, 131.0, 130.7, 128.4, 128.0, 127.9, 127.6, 127.5, 126.7, 125.5 (Ar, C-3 and C-4), 85.6 (C-1′), 75.5 (CH_2Ph), 73.5 (CH_2Ph), 70.4 (C-2′), 69.8 (C-3′), 35.5 (C-2); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{27}H_{27}O_4S$ 447.1630, found 447.1624.

General Procedure for the Synthesis of Thiochromene Derivatives 6a−e. Thiochromenes **6a−e** were synthesized using the same conditions described for the synthesis of **4a**. However, prior to column purification, the thiochromenes so obtained were dispersed in CH_2Cl_2 (5 mL) and treated with acetic anhydride (1 mL), triethylamine (0.5 mL), and a catalytic amount of DMAP. The solution was stirred at room temperature until completion of the reaction (monitored by TLC). The solution was diluted with CH_2Cl_2, washed with water, and dried over $MgSO_4$. The residue was then purified by flash column chromatography on silica gel (ethyl acetate/hexane, 1:9) to afford thiochromene **6a−e** as a yellow syrup:

*(1R,2R)-1,3-Bis(benzyloxy)-1-((S)-3-formyl-2H-thiochromen-2-yl)-propan-2-yl acetate (**6a**):* 129.2 mg, 79% yield; IR (neat cm^{-1}) 1737, 1674, 1626, 1367, 1231, 1140, 1069,732, 696; $[\alpha]_D$ (c 0.1, $CHCl_3$) +15.2; ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (s, 1H, CHO), 7.43−7.10 (m, 13H, Ar and H-4), 6.92−6.80 (m, 2H, Ar), 5.20−5.03 (m, 1H, H-2′), 4.61−4.34 (m, 5H, 2 × CH_2Ph and H-2), 3.88 (t, J = 5.7 Hz, 1H, H-1′), 3.82 (dd, J = 3.5 and 11.0 Hz, 1H, H-3′$_a$), 3.70 (dd, J = 4.8 and 11.0 Hz, 1H, H-3′$_b$), 2.06 (s, 3H, OAc); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.1 (CHO), 169.9 ($OCOCH_3$), 145.8, 137.9, 137.4, 134.5, 132.2, 131.3, 131.0, 130.3, 128.3, 128.0, 127.6, 127.5, 127.1, 125.6 (Ar, C-3 and C-4), 81.3 (C-1′), 74.5 (CH_2Ph), 73.1 (CH_2Ph), 72.1 (C-2′), 67.8 (C-3′), 35.1 (C-2), 21.12 ($OCOCH_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{29}H_{29}O_5S$ 489.1732, found 489.1732.

*(1R,2R)-1,3-Bis(benzyloxy)-1-((S)-3-formyl-6-methyl-2H-thiochromen-2-yl)propan-2-yl acetate (**6b**):* 120.1 mg, 73% yield; IR (neat cm^{-1}) 1737, 1674, 1629, 1566, 1366, 1228, 1143, 1027, 733, 696; $[\alpha]_D$ (c 0.1, $CHCl_3$) +18.5; ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H, CHO), 7.40−6.98 (m, 12H, Ar and H-4), 6.91−6.81 (m, 2H, Ar), 5.13−4.96 (m, 1H, H-2′), 4.55−4.27 (m, 5H, 2 × CH_2Ph and H-2), 3.87−3.78 (m, 2H, H-1′ and H-3′$_a$), 3.69 (dd, J = 4.8 and 10.8 Hz, 1H, H-3′$_b$), 2.28 (s, 3H, CH_3), 2.00 (s, 3H, OAc); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.2 (CHO), 170.0 ($OCOCH_3$), 146.0, 138.0, 137.6, 135.5, 132.4, 132.3, 131.6, 131.0, 130.5, 128.3, 128.0, 127.9, 127.7, 127.6, 127.4, 127.1 (Ar, C-3 and C-4), 81.4 (C-1′), 74.4 (CH_2Ph), 73.2 (CH_2Ph), 72.3 (C-2′), 68.0 (C-3′), 35.2 (C-2), 21.2 ($OCOCH_3$), 20.7 (CH_3); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{30}H_{31}O_5S$ 503.1892, found 503.1878.

*(1R,2R)-1,3-Bis(benzyloxy)-1-((S)-3-formyl-6-methoxy-2H-thiochromen-2-yl)propan-2-yl acetate (**6c**):* 114.2 mg, 69% yield; IR (neat cm^{-1}) 1737, 1676, 1596, 1477, 1370, 1229, 1164, 1025, 731, 697; $[\alpha]_D$ (c 0.1, $CHCl_3$) +12.5; ^1H NMR (400 MHz, $CDCl_3$) δ 9.53 (s, 1H, CHO), 7.39−7.12 (m, 10H, Ar and H-4), 6.93−6.72 (m, 4H, Ar), 5.14−5.01 (m, 1H, H-2′), 4.63−4.24 (m, 5H, 2 × CH_2Ph and H-2), 3.86−3.79 (m, 2H, H-1′ and H-3′$_a$), 3.76 (s, 3H, OMe), 3.69 (dd, J = 6.4 and 12.0 Hz, 1H, H-3′$_b$), 2.01 (s, 3H, OAc); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.1 (CHO), 170.2 ($OCOCH_3$), 158.2, 145.6, 138.2, 133.4, 131.6, 128.3, 128.1, 127.9, 127.7, 127.6, 127.5, 125.1, 117.7, 115.8 (Ar, C-3 and C-4), 81.2 (C-1′), 74.4 (CH_2Ph), 73.2 (CH_2Ph), 72.4 (C-2′), 68.0 (C-3′), 55.5 (OMe), 35.1 (C-2), 21.2 ($OCOCH_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{30}H_{31}O_6S$ 519.1841, found 519.1833.

*(1R,2R)-1,3-Bis(benzyloxy)-1-((S)-6-tert-butyl-3-formyl-2H-thiochromen-2-yl)propan-2-yl acetate (**6d**):* 125.1 mg, 75% yield; IR (neat cm^{-1}) 2958, 1738, 1674, 1622, 1365, 1229, 1138, 1069, 733, 696; $[\alpha]_D$ (c 0.1, $CHCl_3$) +16.3; ^1H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H, CHO), 7.38−7.12 (m, 12H, Ar and H-4), 6.89−6.57 (m, 2H, Ar), 4.98−4.88 (m, 1H, H-2′), 4.49−4.36 (m, 5H, 2 × CH_2Ph and H-2), 3.91 (dd, J = 5.2 and 6.4 Hz, 1H, H-1′), 3.80 (dd, J = 4.4 and 10.8 Hz, H-3′$_a$), 3.70 (dd, J = 4.4 and 10.8 Hz, 1H, H-3′$_b$), 2.03 (s, 3H, OAC), 1.29 (s, 9H, $C(CH_3)_3$); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.3 (CHO), 170.0 ($OCOCH_3$), 148.9, 146.9, 138.0, 137.6, 131.9, 131.3, 130.2, 128.9, 128.4, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 126.8 (Ar, C-3 and C-4), 81.7 (C-1′), 74.7 (CH_2Ph), 73.2 (CH_2Ph), 72.2 (C-2′), 68.0 (C-3′), 35.3 (C-2), 34.4 ($C(CH_3)_3$), 31.2 ($C(CH_3)_3$), 21.2 ($OCOCH_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{33}H_{37}O_5S$ 545.2362, found 545.2362.

*(1R,2R)-1,3-Bis(benzyloxy)-1-((S)-3-formyl-8-methyl-2H-thiochromen-2-yl)propan-2-yl acetate (**6e**):* 118.5 mg, 72% yield; IR (neat cm^{-1}) 1737, 1674, 1629, 1566, 1366, 1228, 1143, 1027, 733, 696; $[\alpha]_D$ (c 0.1, $CHCl_3$) +14.0; ^1H NMR (400 MHz, $CDCl_3$) δ 9.55 (s, 1H, CHO), 7.49−7.08 (m, 12H, Ar and H-4), 6.91−6.89 (m, 2H, Ar), 5.19−5.01 (m, 1H, H-2′), 4.58−4.37 (m, 4H, CH_AH_BPh, CH_AH_BPh and H-2), 4.31 (d, J = 11.2 Hz, 1H, CH_AH_BPh), 3.84−3.77 (m, 2H, H-1′ and H-3′$_a$), 3.70 (dd, J = 5.2 and 10.8 Hz, 1H, H-3′$_b$), 2.35 (s, 3H, CH_3), 1.98 (s, 3H, OAc); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 191.2, (CHO), 170.0 ($OCOCH_3$), 146.3, 138.0, 137.5, 135.9, 133.9, 132.9, 131.8, 130.3, 128.9, 128.3, 128.1, 127.9, 127.6, 127.5, 124.8 (Ar, C-3 and C-4), 81.4 (C-1′), 74.5 (CH_2Ph), 73.2 (CH_2Ph), 72.4 (C-2′), 68.0 (C-3′), 35.2 (C-2), 21.1 ($OCOCH_3$), 20.3 (CH_3); HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{30}H_{31}O_5S$ 503.1892, found 503.1883.

General Procedure for the Synthesis of Thiochroman Sulfoxide Derivatives 13a−e. To a vigorously stirring suspension of wet alumina (1.11 g wetted with 117 μL of water) and Oxone (332 mg, 0.54 mmol) in DCM was added thiochroman **12** (0.54 mmol). After 3 h of stirring at room temperature, the adsorbent was filtered over a Celite bed and washed several times with DCM. The filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 4:6) to give the corresponding diastereomeric sulfoxides:

*(2R,3S,4R,4aR,10bR)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**13a**, first diastereomer):* 134.8 mg, 45% yield; colorless oil; $[\alpha]_D$ (c 0.1, $CHCl_3$) −33.5; IR (neat, cm^{-1}) 1028, 696; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, J = 7.2 Hz, 1H), 7.65−7.00 (m, 18H), 4.91 (d, J = 10.8 Hz, 1H), 4.80 (d, J = 11.6 Hz, 1H), 4.65−4.30 (m, 5H), 4.10−3.90 (m, 1H), 3.80−3.50 (m, 5H), 3.36 (d, J = 13.2 Hz, 1H), 3.15 (t, J = 13.0 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 137.6, 133.4, 132.7, 132.3, 131.6, 130.0, 128.5, 128.4, 128.3, 128.0, 128.0, 127.8, 127.7, 127.6, 81.0, 79.8, 75.2, 74.5, 73.5, 73.4, 70.8, 69.2, 40.2, 28.3; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{34}H_{35}O_5S$ 555.2205, found 555.2200.

*(2R,3S,4R,4aR,10bR)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**13a** second diastereomer).* 59.9 mg, 20% yield; white solid; mp 115−117 °C; $[\alpha]_D$ (c 0.1, $CHCl_3$) +24.5; IR (neat, cm^{-1}) 1026, 695; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.85 (d, J = 7.6 Hz, 1H), 7.70−7.00 (m, 18H), 4.86

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(d, J = 10.8 Hz, 1H), 4.70 (s, 2H), 4.60−4.30 (m, 4H), 4.00−3.50 (m, 6H), 3.40−3.20 (m, 1H), 2.60−2.40 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 142.5, 138.1, 138.1, 137.7, 133.6, 131.8, 130.6, 130.0, 128.6, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.7, 127.6, 127.0, 81.5, 80.4, 75.2, 74.6, 73.6, 73.5, 72.1, 69.2, 42.3, 34.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{34}H_{35}O_5S$ 555.2205, found 555.2205.

*(2R,3S,4R,4aR,10bR)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-9-methyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**13b**, first diastereomer):* 153.6 mg, 50% yield; colorless oil; $[\alpha]_D$ (c 0.1, $CHCl_3$) −20; IR (neat, cm^{-1}) 1027, 695; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.62 (d, J = 8.4 Hz, 1H), 7.50−7.00 (m, 17H), 4.91 (d, J = 10.8 Hz, 1H), 4.81 (d, J = 11.2 Hz, 1H), 4.65−4.35 (m, 5H), 4.10−3.90 (m, 1H), 3.80−3.50 (m, 5H), 3.36 (d, J = 13.6 Hz, 1H), 3.11 (t, J = 13.0 Hz, 1H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 143.0, 138.3, 138.1, 137.6, 134.7, 133.3, 133.2, 131.6, 130.7, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 81.1, 79.8, 75.2, 74.6, 73.5, 73.4, 70.7, 69.3, 40.1, 28.2, 21.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{35}H_{37}O_5S$ 569.2362, found 569.2365.

*(2R,3S,4R,4aR,10bR)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-9-methyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**13b**, second diastereomer):* 67.6 mg, 22% yield; white solid; mp 99−101 °C; $[\alpha]_D$ (c 0.1, $CHCl_3$) +7.5; IR (neat, cm^{-1}) 1026, 696; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, J = 8.0 Hz, 1H), 7.50−7.10 (m, 17H), 4.88 (d, J = 10.8 Hz, 1H), 4.73 (s, 2H), 4.65−4.42 (m, 3H), 4.37 (s, 1H), 3.90−3.50 (m, 6H), 3.40−3.20 (m, 1H), 2.60−2.43 (m, 1H), 2.40 (s, 3H,); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 141.0, 138.5, 138.1, 138.0, 137.7, 133.4, 132.3, 130.9, 128.6, 128.4, 128.3, 128.0, 127.8, 127.7, 127.6, 127.0, 81.6, 80.3, 75.2, 74.6, 73.7, 73.4, 72.1, 69.2, 42.4, 34.5, 21.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{35}H_{37}O_5S$ 569.2362, found 569.2365

*(2R,3S,4R,4aR,10bR)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-9-methoxy-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**13c**):* 94.7 mg, 30% yield; colorless oil; $[\alpha]_D$ (c 0.1, $CHCl_3$) −15.5; IR (neat, cm^{-1}) 1028, 697; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.59 (d, J = 8.4 Hz, 1H), 7.40−7.05 (m, 15H), 7.00−6.80 (m, 2H), 4.85 (d, J = 10.8 Hz, 1H), 4.74 (d, J = 11.6 Hz, 1H), 4.60−4.30 (m, 5H), 4.10−3.90 (m, 1H), 3.85−3.45 (m, 8H), 3.30 (d, J = 13.6 Hz, 1H), 3.00 (t, J = 13.2 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 126.5, 138.2, 138.1, 137.6, 135.3, 133.5, 128.4, 128.3, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 117.6, 115.8, 81.0, 79.8, 75.1, 74.5, 73.6, 73.4, 70.7, 69.3, 55.6, 40.0, 27.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{35}H_{37}O_6S$ 585.2311, found 585.2313.

*(2R,3S,4R,4aR,10bR)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-9-tert-butyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**13d**, first diastereomer):* 214.4 mg, 65% yield; colorless oil; $[\alpha]_D$ (c 0.1, $CHCl_3$) −28.5; IR (neat, cm^{-1}) 1051, 683; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, J = 8.0 Hz, 1H), 7.60−7.10 (m, 17H), 4.91 (d, J = 10.8 Hz, 1H), 4.80 (d, J = 11.6 Hz, 1H), 4.65−4.35 (m, 5H), 4.10−3.90 (m, 1H), 3.80−3.50 (m, 5H), 3.36 (d, J = 12.4 Hz, 1H), 3.13 (t, J = 13.0 Hz, 1H), 1.31 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 156.0, 138.3, 138.1, 137.6, 134.7, 132.9, 131.4, 129.7, 128.5, 128.4, 128.3, 128.0, 128.0, 127.8, 127.7, 127.7, 127.6, 127.3, 81.1, 79.8, 75.2, 74.6, 73.8, 73.4, 70.7, 69.2, 40.2, 35.1, 31.1, 28.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{38}H_{43}O_5S$ 611.2831, found 611.2828.

*(2R,3S,4R,4aR,10bR)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-9-tert-butyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**13d**, second diastereomer):* 82.4 mg, 25% yield; white solid; mp 136−138 °C; $[\alpha]_D$ (c 0.1, $CHCl_3$) +10.0; IR (neat, cm^{-1}) 1051, 683; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, J = 8.4 Hz, 1H), 7.60−7.10 (m, 17H), 4.86 (d, J = 10.8 Hz, 1H), 4.70 (s, 2H), 4.60−4.40 (m, 3H), 4.37 (s, 1H), 3.90−3.50 (m, 6H), 3.40−3.20 (m, 1H), 2.60−2.40 (m, 1H), 1.31 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 154.1, 139.4, 138.2, 138.1, 137.7, 133.3, 128.7, 128.6, 128.4, 128.3, 128.0, 127.8, 127.8, 127.6, 127.5, 127.3, 126.9, 81.6, 80.4, 75.2, 74.7, 73.9, 73.4, 72.1, 69.2, 42.4, 34.8, 34.6, 31.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{38}H_{43}O_5S$ 611.2831, found 611.2828.

*(2R,3S,4R,4aR,10bR)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**13e**, first diastereomer):* 153.6 mg, 50% yield; colorless oil; $[\alpha]_D$ (c 0.1, $CHCl_3$) −24.6; IR (neat, cm^{-1}) 1027, 695; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.50−7.00 (m, 18H), 4.92 (d, J = 10.4 Hz, 1H), 4.81 (d, J = 11.2 Hz, 1H), 4.65−4.35 (m, 5H), 4.10−3.90 (m, 1H), 3.80−3.50 (m, 5H), 3.43 (d, J = 14.0 Hz, 1H), 3.06 (t, J = 13.4 Hz, 1H), 2.72 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 140.3, 138.3, 138.1, 137.6, 135.6, 133.6, 132.0, 130.9, 128.5, 128.3, 128.3, 128.1, 127.9, 127.8, 127.8, 127.7, 127.6, 81.0, 79.7, 75.2, 74.5, 73.8, 73.4, 70.7, 69.2, 39.3, 27.5, 18.8; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{35}H_{37}O_5S$ 569.2362, found 569.2366.

*(2R,3S,4R,4aR,10bR)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,4a,5,10b-hexahydro-S-oxothiochromeno[4,3-b]pyran (**13e**, second diastereomer):* 76.8 mg, 25% yield; oil; $[\alpha]_D$ (c 0.1, $CHCl_3$) +11.6; IR (neat, cm^{-1}) 1026, 696; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.50−7.00 (m, 18H), 4.85 (d, J = 10.4 Hz, 1H), 4.69 (s, 2H), 4.60−4.40 (m, 3H), 4.31 (s, 1H), 3.95−3.30 (m, 6H), (m, 1H), 2.67 (s, 3H), 2.55−2.40 (m, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 140.4, 139.1, 138.2, 138.1, 137.8, 134.5, 132.6, 130.3, 128.6, 128.4, 128.3, 128.0, 128.0, 127.8, 127.6, 127.5, 81.6, 80.4, 75.2, 74.5, 74.4, 73.5, 71.9, 69.2, 42.6, 34.4, 21.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{35}H_{37}O_5S$ 569.2362, found 569.2366.

General procedure for the Synthesis of Thiochromene Derivatives 20a−e. NaOAc (4 mg, 0.03 mmol) was added to a solution of sulfoxide **13** (0.30 mmol) in acetic anhydride (2 mL), and the reaction mixture was stirred overnight at 140 °C. The reaction mixture was then allowed to cool to room temperature and diluted with DCM. The resulting solution was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 5:95) to yield the corresponding thiochromene **20**:

*(2R,3S,4R,10aS)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-2,3,4,10a-tetrahydrothiochromeno[2,3-b]pyran (**20a**):* 161.0 mg, 63% yield; white solid; mp 66−68 °C; $[\alpha]_D$ (c 0.5, $CHCl_3$) −96.5; IR (neat, cm^{-1}) 696; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60−7.00 (m, 19H, Ar), 6.75 (d, J = 1.2 Hz, 1H, H-5), 5.25 (s, 1H, H-10a), 5.00−4.80 (m, 2H, CH_2Ph), 4.71 (d, J = 11.6 Hz, 1H, CH_2Ph), 4.60−4.40 (m, 3H, CH_2Ph), 4.26 (dd, J = 1.6 and 8.4 Hz, 1H, H-4), 3.80−3.40 (m, 4H, H-3, H-1′$_a$, H-1′$_b$, H-2); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 138.0, 137.8, 129.6, 128.6, 128.5, 128.4, 128.3, 128.3, 128.3, 128.2, 128.0, 128.0, 127.9, 127.8, 127.8, 127.8, 127.7, 127.6, 125.6, 125.2 (Ar and C-4a), 120.4 (C-5), 85.1 (C-4), 82.2 (C-3), 80.6 (C-2), 75.4 (C-10a), 75.2, 73.5, 72.8 (CH_2Ph), 69.1 (C-1′); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{34}H_{33}O_4S$ 537.2100, found 537.2100.

*(2R,3S,4R,10aS)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-7-methyl-2,3,4,10a-tetrahydrothiochromeno[2,3-b]pyran (**20b**):* 142.1 mg, 86% yield; white solid; mp 109−111 °C; $[\alpha]_D$ (c 0.5, $CHCl_3$) −95.5; IR (neat, cm^{-1}) 696; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60−6.90 (m, 18H, Ar), 6.72 (s, 1H, H-5), 5.23 (s, 1H, H-10a), 5.00−4.80 (m, 2H, CH_2Ph), 4.72 (d, J = 11.6 Hz, 1H, CH_2Ph), 4.60−4.40 (m, 3H, CH_2Ph), 4.27 (d, J = 8.4 Hz, 1H, H-4), 3.80−3.50 (m, 4H, H-3, H-1′$_a$, H-1′$_b$, H-2), 2.30 (s, 3H, ArCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 138.0, 137.9, 134.9, 130.2, 129.2, 128.5, 128.3, 128.2, 128.0, 127.9, 127.9, 127.7, 127.5, 127.4, 125.4, 125.0 (Ar and C-4a), 120.5 (C-5), 85.1 (C-4), 82.2 (C-3), 80.5 (C-2), 75.5 (C-10a), 75.2, 73.4, 72.7 (CH_2Ph), 69.1 (C-1′), 20.8 (ArCH_3); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{35}H_{35}O_4S$ 551.2256, found 551.2258. The compound was crystallized from a mixture of ethyl acetate and hexane for X-ray analysis.

*(2R,3S,4R,10aS)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-7-methoxy-2,3,4,10a-tetrahydrothiochromeno[2,3-b]pyran (**20c**):* 102.0 mg, 60% yield; white solid; mp 126−128 °C; $[\alpha]_D$ (c 0.5, $CHCl_3$) −99.5; IR (neat, cm^{-1}) 697; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.50−7.00 (m, 16H, Ar), 6.85−6.75 (m, 2H, Ar), 6.70 (d, J = 1.6 Hz, 1H, H-5), 5.20 (s, 1H, H-10a), 4.95−4.80 (m, 2H, CH_2Ph), 4.72 (d, J = 11.6 Hz, 1H, CH_2Ph), 4.60−4.35 (m, 3H, CH_2Ph), 4.27 (dd, J = 1.2 and 8.4 Hz, 1H, H-4), 3.90−3.40 (m, 7H, OCH_3, H-3, H-1′$_a$, H-2′$_b$, H-2); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 157.6, 138.1, 137.9, 129.1, 128.6, 128.4, 128.3, 128.0, 128.0, 127.9, 127.8, 127.6, 126.6, 120.5, 119.3, 115.0, 114.6 (Ar, C-4a and C-5), 85.1 (C-4), 82.3 (C-3), 80.6 (C-2), 75.6 (C-10a), 75.3, 73.5, 72.8 (CH_2Ph), 69.1 (C-1′), 55.5 (OCH_3); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{35}H_{35}O_5S$ 567.2205, found 567.2209. The compound was crystallized from ethanol for X-ray analysis.

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*(2R,3S,4R,10aS)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-7-tert-butyl-2,3,4,10a-tetrahydrothiochromeno[2,3-b]pyran (**20d**):* 117.3 mg, 66% yield; white solid; mp 122−124 °C; $[\alpha]_D$ (*c* 0.5, $CHCl_3$) −164.0; IR (neat, cm^{-1}) 696; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60−7.00 (m, 18H, Ar), 6.75 (s, 1H, H-5), 5.22 (s, 1H, H-10a), 4.92 (d, J = 12.0 Hz, 2H, CH_2Ph), 4.72 (d, J = 112.0 Hz, 1H, CH_2Ph), 4.60−4.40 (m, 3H, CH_2Ph), 4.26 (d, J = 8.4 Hz, 1H, H-4), 3.80−3.40 (m, 4H, H-3, H-1′$_a$, H-1′$_b$, H-2), 1.30 (s, 9H, $(C(CH_3)_3)$; $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 148.4, 138.1, 138.0, 128.6, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.7, 127.5, 127.2, 126.7, 125.7, 125.3, 125.1 (Ar and C-4a), 121.0 (C-5), 85.1 (C-4), 82.3 (C-3), 80.6 (C-2), 75.5 (C-10a), 75.2, 73.5, 72.8 (CH_2Ph), 69.2 (C-1′), 34.4 ($C(CH_3)_3$), 31.3 ($C(CH_3)_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{38}H_{41}O_4S$ 593.2726, found 593.2720. The compound was crystallized from a mixture of ethyl acetate and hexane for X-ray analysis.

*(2R,3S,4R,10aS)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-9-methyl-2,3,4,10a-tetrahydrothiochromeno[2,3-b]pyran (**20e**):* 140.0 mg, 85% yield; oil; $[\alpha]_D$ (*c* 0.5, $CHCl_3$) −88.0; IR (neat, cm^{-1}) 696; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60−6.90 (m, 18H, Ar), 6.74 (d, J = 1.6 Hz, 1H, H-5), 5.34 (s, 1H, H-10a), 5.00−4.80 (m, 2H, CH_2Ph), 4.71 (d, J = 11.6 Hz, 1H, CH_2Ph), 4.60−4.40 (m, 3H, CH_2Ph), 4.25 (dd, J = 1.2, and 8.4 Hz, 1H, H-4), 3.80−3.40 (m, 4H, H-3, H-1′$_a$, H-1′$_b$, H-2), 2.32 (s, 3H, $ArCH_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 138.1, 138.0, 137.9, 133.7, 130.0, 128.6, 128.4, 128.3, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 127.6, 127.6, 127.2, 124.4, 121.0 (Ar, C-4a and C-5), 85.0 (C-4), 82.1 (C-3), 80.6 (C-2), 75.3 (C-10a), 75.2, 73.4, 72.8 (CH_2Ph), 69.1 (C-1′), 19.5 ($ArCH_3$); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{35}H_{35}O_4S$ 551.2256, found 551.2260.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and $^{13}C\{^1H\}$ NMR spectra for products **4a**, **5a−e**, **6a−e**, **13a−e**, and **20a−e**; COSY and HSQC spectra for **4a**, **6a**, and **20a**; crystallographic data for the structures of **20b−d** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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