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# Regiospecific Synthesis of 2-Halo-3-(2′-glucalyl)benzo[*b*]thiophenes

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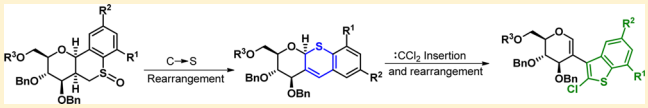
Supporting Information

**ABSTRACT:** A regiospecific synthetic strategy for the synthesis of 2-chloro-3-substituted benzo[*b*]thiophenes is developed via a dichlorocarbene insertion and sigmatropic rearrangement of an in situ generated ylide. The current protocol provides a reversed regiochemistry to the commonly employed electrophilic cyclization reaction for the synthesis of benzo[*b*]thiophenes and access to their hitherto underrepresented chlorinated derivatives.




Benzo[*b*]thiophenes are aromatic annulated sulfur-containing five-membered heterocyclic derivatives. They have attracted substantial attention due to their presence as key structural components in a number of important compounds that possess a wide range of biological activities including antifungal,[1−3] antibacterial,[2,3] antiinflammatory,[2−4] anticancer,[5,6] and antiallergy.[7] Raloxifene, Arzoxifene, Zileuton, and Sertaconazole are examples of benzo[*b*]thiophene-containing clinically used drugs. Furthermore, a sugar-linked benzo[*b*]thiophene, Ipragliflozin,[8−10] has been recently approved in Japan for the treatment of type 2 diabetes. Owing to their important biological activities, a number of efficient methodologies for the synthesis of benzo[*b*]thiophenes have been developed. Transition-metal-catalyzed annulations[11−14] and electrophilic cyclization[15−20] are among the commonly employed methodologies for the synthesis of such compounds. The former methodology provides 2-substituted or 2,3-disubstituted benzo[*b*]thiophenes depending on the alkyne substrate employed, while the latter furnishes 3-halo-2-substituted products. Considering the high cost of the transition metal catalysts and the possibility of transforming the halide moiety of the benzo[*b*]thiophenes into different analogues using Suzuki, Sonogashira, Heck, Negishi, Kumada, Hiyama, Fukuyama, Stille, and Buchwald−Hartwig reactions, the electrophilic cyclization reaction is the preferred protocol for their synthesis.[19,21] Although a number of reagent systems are reported for the synthesis of 3-iodo/bromo-2-substituted benzo[*b*]thiophenes, chloro- and fluorocyclizations using appropriate electrophiles as well as attempts to construct 2-halo-3-substituted regioisomers (reversed regioisomers in respect of the outcome of normal electrophilic cyclization) of benzo[*b*]thiophenes are less explored.[21,22] The search for the chloro- and fluorocyclization methodologies is interesting since the nature of halogen substituents is reported to affect the adsorption, metabolism, distribution, and excretion properties of bioactive molecules.[21] In continuation of our previous studies on the stereoselective synthesis of carbohydrate fused-thiochromans and thiochromenes,[23−25] we report herein the successful synthesis of the privileged 2-chloro-3-(2′-glucalyl)-benzo[*b*]thiophenes via a sigmatropic allylic rearrangement of the ylide intermediate of a serendipitously formed aryl-*S*-glucoside. Incorporation of the glucalyl moiety with its inherently defined stereochemistry adds potential for further structural elaborations.

We recently reported that treatment of sulfoxide **1** with NaOAc in acetic anhydride resulted in the formation of an unexpected fused aryl-*S*-glucoside **2**, presumably via an unusual C → S rearrangement reaction as shown in Scheme 1,[25] and this provided the substrate for the benzothiophene synthesis in the current study.

Various aryl-*S*-glucosides were prepared by the C → S rearrangement reaction in order to assess the scope and generality of our approach. In all cases complete conversion of the starting sulfoxides to their corresponding fused aryl-*S*-glucosides was achieved, and products were identified by $^{1}$H and $^{13}$C NMR as well as HRMS spectra after chromatographic purification. Although a range of different protecting groups on the sugar moiety and substituents on the arylthiol moiety were found to be compatible, the synthesis of the diastereomeric galactosyl analogues could not be achieved, presumably due to the 1,3-diaxial strain experienced during substitution of the iodide with the arylthiolate to prepare the thiochroman substrate.[23]

After establishing the generality of the rearrangement reaction with glucosyl sugar analogues, our attention turned to the application of the resulting aryl-*S*-glucosides in the synthesis of benzo[*b*]thiophenes. Parham et al. and later Moss et al. reported that dichlorocarbene, phenylchlorocarbene, and phenylfluorocarbene react with acyclic allylic sulfides to produce C−S insertion products via initial formation of sulfonium ylides that subsequently undergo [2,3] sigmatropic rearrangement in preference to cyclopropanation of the allylic double bond, which is the case with allylic ethers.[26−29] Although the methodology is unique and efficient, it has not, to the best of our knowledge, been extensively applied in the synthesis of complex organic molecules. These interesting results prompted us to attempt the dichlorocarbene reaction on

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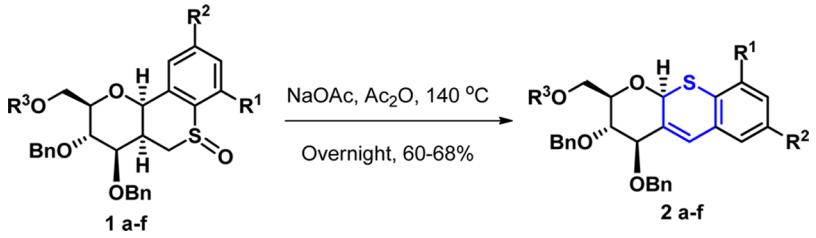
**Scheme 1. C → S Rearrangement Reaction**




our aryl-*S*-glucosides. It was envisioned that the nucleophilic sulfur in the highly conjugated system of the aryl-*S*-glucoside **2** would react with the electrophilic dichlorocarbene with subsequent sigmatropic rearrangement to provide the benzo[*b*]thiophenes. In pursuit of this goal, aryl-*S*-glucoside **2a** was treated with a 1:1 mixture of 50% aqueous NaOH and $CHCl_3$, in the presence of benzyltriethylammonium chloride as a phase-transfer catalyst to provide benzo[*b*]thiophene **3a** in 67% yield. The structure of the benzo[*b*]thiophene **3a** was established using NMR and HRMS spectra. Evidence included the appearance of the downfield singlet for the anomeric proton at $\delta_H$ 6.52 and the resonances of C-1′ and C-2′ at $\delta_C$ 145.6 and 106.0, respectively, representing a typical pattern of a glucal system. The HMBCAD (heteronuclear multiple bond correlation adibatic) spectrum displayed correlation of H-1′ with C-2′, C-3′, and C-5′ of the glucal moiety as well as the C-3 of the benzo[*b*]thiophene group, suggesting the cleavage of the bond between the anomeric carbon and the sulfur. The upfield shift of the AB system of the $CH_2$ protons that corresponds to the benzyl protecting group at C-3′ suggest the restricted free-rotation of the benzoloxy group due to the close proximity of the highly aromatized benzo[*b*]thiophene moiety and anisotropy shielding as they lie below this aromatic ring. The mass spectrometry exhibited a molecular ion of [M + Na] 605.1537, which corresponds to the calculated value of 605.1529. The $[M + Na]^+$ (605.1537) and $[M + Na]^+ + 2$ (607.1515) pattern of the mass spectrometer also suggests the presence of one chlorine atom in the molecule.

In order to evaluate the generality and scope of the proposed synthesis of the benzo[*b*]thiophene derivatives, the reaction was monitored with a number of aryl-*S*-glucosides. The reaction provided the corresponding *glucal* derived 2-chloro-3-substituted benzo[*b*]thiophenes in moderate yields, and the results are summarized in Table 1. The reaction conditions are tolerant of both *O*-acetate and *O*-benzyl protecting groups as well as a variety of aromatic substituents. In all cases complete conversion of the starting glucoside to the corresponding benzo[*b*]thiophenes was achieved, and products were identified by $^1H$ and $^{13}C$ NMR spectroscopy after chromatographic purification. It was interesting to note that no deacetylated product was isolated during the reaction of the monoacetylated glucoside **2f**.

**Table 1. Synthesis of 2-Halo-3-(2′-glucalyl)benzo[*b*]thiophenes 3a−h**

| entry | aryl-*S*-glucosides **2a−f** | benzo[*b*]thiophenes **3a−h** | yield (%) |
|---|---|---|---|
| 1 | **2a** $R^1 = R^2 = H$, $R^3 = Bn$ | **3a** $R^1 = R^2 = H$, $R^3 = Bn$, X = Cl | 67 |
| 2 | **2b** $R^1 = H$, $R^2 = CH_3$, $R^3 = Bn$ | **3b** $R^1 = H$, $R^2 = CH_3$, $R^3 = Bn$, X = Cl | 68 |
| 3 | **2c** $R^1 = H$, $R^2 = OCH_3$, $R^3 = Bn$ | **3c** $R^1 = H$, $R^2 = OCH_3$, $R^3 = Bn$, X = Cl | 65 |
| 4 | **2d** $R^1 = H$, $R^2 = C(CH_3)_3$, $R^3 = Bn$ | **3d** $R^1 = H$, $R^2 = C(CH_3)_3$, $R^3 = Bn$, X = Cl | 72 |
| 5 | **2e** $R^1 = CH_3$, $R^2 = H$, $R^3 = Bn$ | **3e** $R^1 = CH_3$, $R^2 = H$, $R^3 = Bn$, X = Cl | 64 |
| 6 | **2f** $R^1 = R^2 = H$, $R^3 = Ac$ | **3f** $R^1 = R^2 = H$, $R^3 = Ac$, X = Cl | 68 |
| 7 | **2a** $R^1 = R^2 = H$, $R^3 = Bn$ | **3g** $R^1 = R^2 = H$, $R^3 = Bn$, X = Br | 61 |
| 8 | **2f** $R^1 = R^2 = H$, $R^3 = Ac$ | **3h** $R^1 = R^2 = H$, $R^3 = Ac$, X = Br | 60 |

The possibility of using this methodology for the synthesis of the bromo analogues was demonstrated by replacement of $CHCl_3$ with $CHBr_3$ in reactions of glucosides **2a** and **2f** (Scheme 2 and Table 1, entries 7 and 8), though the yields were relatively lower than those obtained for the chloro analogues. In contrast to the attempted cyclopropanation of glycals with dibromocarbenes reported by Nagarajan et al.,[30] the insertion of the dibromocarbene to substrates **2a** and **2f** followed by the rearrangement reaction to yield the brominated benzothiophenes proceeded smoothly without the reaction mixture turning black and viscous.

The proposed mechanism for the formation of the benzo[*b*]thiophenes **3** is outlined in Scheme 3. The reaction is proposed to proceed via initial formation of the ylide **I**.[26] Sigmatropic rearrangement facilitates the cleavage of the C−S bond to form the dichlorinated benzothiophane **II**. Abstraction of the acidic proton by the base present in the reaction mixture with the subsequent elimination of one of the chlorine atoms provides the aromatized benzo[*b*]thiophene **3**.

In conclusion, the unusual C → S rearrangement reaction of sulfoxides **1a−f** to provide aryl-*S*-glucosides **2a−f** was realized. The aryl-*S*-glucosides so obtained are successfully employed in the synthesis of novel 2-halo-3-glucalyl substituted benzo[*b*]thiophenes **3a−h**. The current protocol provides alternative access to the under-represented synthesis of chlorinated benzo[*b*]thiophenes as well as the 2-halo-3-substituted regioisomers. Considering the ease of preparation of the substrates and possibilities for further elaboration of the carbohydrate moieties with their well-defined inherent stereochemistry, the current strategy for synthesis of benzo[*b*]thiophene derivatives would be of great benefit to medicinal chemists.

## EXPERIMENTAL SECTION

All solvents were dried by appropriate techniques reported by Perrin and Armarego.[31] Sulfoxides **1a−e** and aryl-*S*-glycosides **2a−e** were synthesized according to previously published protocols.[25] All reactions were monitored by thin layer chromatography (TLC) on 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% sulfuric acid in ethanol and then baking at 150 °C. Gravity column chromatography was done on silica gel 60 (70−230 mesh). 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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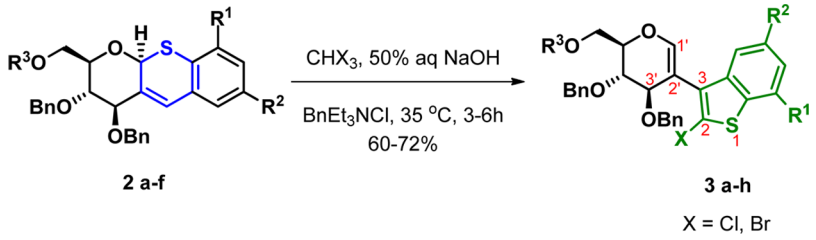
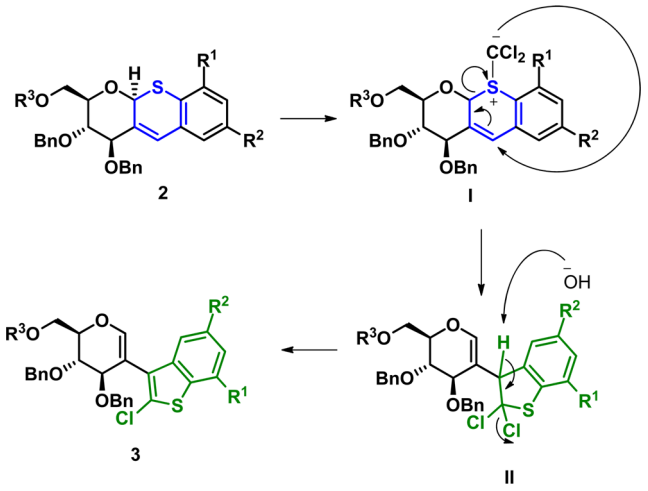
**Scheme 2. Synthesis of 2-Halo-3-(2′-glucalyl)-benzo[*b*]thiophenes**




**Scheme 3. Proposed Mechanism for the Synthesis of the Benzo[*b*]thiophenes**




were recorded as deuteriochloroform solutions using tetramethylsilane as an internal standard. All chemical shifts are reported in ppm.

**((2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2,3,4,10a-tetrahydrothiochromeno[2,3-*b*]pyran-2-yl)methyl Acetate (2f).** To a solution of (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[23] (500 mg, 0.928 mmol) in $Ac_2O$ (3 mL) was added a solution of $H_2SO_4$ in $Ac_2O$ (2% v/v, 3.5 mL), and the reaction mixture was stirred at room temperature for 15 min. The reaction mixture was then poured into an ice-cold saturated aqueous $NaHCO_3$ with vigorous stirring. The aqueous solution was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane, 1:9) to obtain the monoacetylated (2*R*,3*S*,4*R*,4a*R*,10b*R*)-3,4-bis(benzyloxy)-2,3,4,4a,5,10b-hexahydrothiochromeno[4,3-*b*]pyran-2-yl)methyl acetate: 400 mg, 88% yield; colorless oil; IR (neat $cm^{-1}$) 1737, 1072, 733, 696; $[\alpha]_D$ (*c* 0.5, $CHCl_3$) +28.1; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.47−6.99 (m, 14H), 4.92 (d, *J* = 10.8 Hz, 1H), 4.76 (d, *J* = 11.6 Hz, 1H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 10.8 Hz, 1H), 4.37 (s, 1H), 4.28−4.21 (m, 2H), 3.94 (dd, *J* = 5.2 and 8.8 Hz, 1H), 3.68 (ddd, *J* = 2.4, 3.6, and 9.4 Hz, 1H), 3.61 (t, *J* = 9.4 Hz, 1H), 3.23 (t, *J* = 12.8 Hz, 1H), 2.97 (dd, *J* = 1.4 and 12.8 Hz, 1H), 2.63 (ddd, *J* = 2.4, 5.2, and 10.4 Hz, 1H), 1.98 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ 170.8, 137.9, 137.8, 134.0, 133.2, 130.6, 129.0, 128.5, 128.2, 127.9, 127.7, 126.5, 124.3, 82.8, 75.1, 74.3, 73.8, 71.2, 63.7, 38.8, 21.1, 20.9; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{29}H_{30}NaO_5S$ 513.1712, found 513.1716. This monoacetylated product (350 mg, 0.71 mmol) was then added to a vigorously stirring suspension of wet alumina (1.11 g wetted with 117 $\mu$L of water) and OXONE (437 mg, 0.71 mmol) in $CH_2Cl_2$ (5 mL). After 3 h of stirring at room temperature, the adsorbent was filtered over a Celite bed and washed several times with $CH_2Cl_2$. The filtrate was evaporated *in vacuo*. NaOAc (8 mg, 0.06 mmol) was added to a solution of the solid residue in $Ac_2O$ (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 $CH_2Cl_2$. The resulting solution was washed successively with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and evaporated. The residue product was purified by column chromatography on silica gel (ethyl acetate/hexane, 10:90) to provide the title compound **2f**: 210 mg, 60% yield; colorless oil; IR (neat $cm^{-1}$) 1736, 1087, 733, 696; $[\alpha]_D$ (*c* 0.5, $CHCl_3$) −65.7; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.51−7.06 (m, 14H), 6.78 (s, 1H), 5.26 (s, 1H), 4.98 (d, *J* = 10.8 Hz, 1H), 4.90 (d, *J* = 11.6 Hz, 1H), 4.73 (d, *J* = 11.6 Hz, 1H), 4.60 (d, *J* = 10.8 Hz, 1H), 4.30 (bd, *J* = 7.6 Hz, 1H), 4.25 (dd, *J* = 2.0 and 12.2 Hz, 1H), 4.16 (dd, *J* = 5.2 and 12.2 Hz, 1H), 3.78 (ddd, *J* = 2.0, 5.2, and 9.6 Hz, 1H), 3.50 (dd, *J* = 8.6 and 9.6 Hz, 1H), 1.96 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ 170.8, 137.6, 129.7, 128.6, 128.5, 128.4, 128.2, 128.0, 127.8, 127.7, 127.4, 125.7, 125.4, 120.7, 85.0, 81.6, 78.4, 75.4, 75.3, 72.8, 63.5, 20.9; HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{29}O_5S$ 489.1736, found 489.1746.

**General Procedure for the Synthesis of Benzothiophenes 3.** 50% aq NaOH (5 mL) was added to a vigorously stirred solution of aryl-*S*-glucoside **2** (0.28 mmol) in $CHCl_3$ or $CHBr_3$ (5 mL) containing $BnEt_3NCl$ (0.088 mmol). After stirring at 35 °C for 6 h (for the $CHCl_3$ solution) or 3 h (for the $CHBr_3$ solution), the reaction mixture was diluted with water, and the aqueous phase was extracted with $CH_2Cl_2$ (4 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated *in vacuo*. Chromatography on silica gel (ethyl acetate/hexane, 3:97) of the residue gave the corresponding benzo[*b*]thiophenes **3**:

**(2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-5-(2-chlorobenzo[*b*]thiophen-3-yl)-3,4-dihydro-2*H*-pyran (3a).** 111 mg, 67% yield; colorless oil; IR (neat $cm^{-1}$) 1652, 1065, 731, 695; $[\alpha]_D$ (*c* 0.5, $CHCl_3$) +20.2; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.70−7.65 (m, 1H, Ar), 7.64−7.58 (m, 1H, Ar), 7.40−7.22 (m, 12H, Ar), 7.19−7.01 (m, 3H, Ar), 6.77 (d, *J* = 6.4 Hz, 2H, Ar), 6.52 (s, 1H, H-1′), 4.78 (d, *J* = 11.6 Hz, 1H, $CH_AH_BPh$), 4.68 (d, *J* = 11.6 Hz, $CH_AH_BPh$), 4.63 (d, *J* = 12.0 Hz, 1H, $CH_AH_BPh$), 4.59 (d, *J* = 12.0 Hz, 1H, $CH_AH_BPh$), 4.47−4.41 (m, 2H, H-3′ and H-5′), 4.28 (d, *J* = 11.6 Hz, 1H, $CH_AH_BPh$), 4.12 (d, *J* = 11.6 Hz, 1H, $CH_AH_BPh$), 4.03 (t, *J* = 5.6 Hz, 1H, H-4′), 3.99 (dd, *J* = 6.2 and 10.6 Hz, 1H, H-$6_a$′), 3.81 (dd, *J* = 3.4 and 10.6 Hz, 1H, H-$6_b$′); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ 145.6, 139.3, 137.9, 137.7, 137.0, 129.9, 129.6, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 124.8, 124.7, 123.0, 121.6, 106.0, 76.8, 74.9, 74.1, 73.5, 73.1, 72.3, 68.2; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{35}H_{31}ClNaO_4S$ 605.1529, found 605.1537; $[M + NH_4]^+$ calcd for $C_{35}H_{35}ClNO_4S$ 600.1975, found 600.1973.

**(2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-5-(2-chloro-5-methyl benzo[*b*]thiophen-3-yl)-3,4-dihydro-2*H*-pyran (3b).** 115 mg, 68% yield; colorless oil; IR (neat $cm^{-1}$) 1650, 1095, 733, 696; $[\alpha]_D$ (*c* 0.5, $CHCl_3$) +12.6; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.54 (d, *J* = 8.4 Hz, 1H), 7.42 (s, 1H), 7.40−7.20 (m, 11H), 7.14−7.02 (m, 3H), 6.83−6.75 (m, 2H), 6.50 (s, 1H), 4.77 (d, *J* = 11.6 Hz, 1H), 4.67 (d, *J* = 11.6 Hz, 1H), 4.63−4.56 (m, 2H), 4.48−4.38 (m, 2H), 4.28 (d, *J* = 11.2 Hz, 1H), 4.12 (d, *J* = 11.2 Hz, 1H), 4.04 (dd, *J* = 5.0 and 6.6 Hz, 1H), 3.97 (dd, *J* = 5.8 and 10.6 Hz, 1H), 3.82 (dd, *J* = 3.6 and 10.6 Hz, 1H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ 145.6, 139.4, 137.9, 137.8, 134.5, 134.1, 129.5, 128.5, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.6, 127.3, 126.4, 122.9, 121.3, 106.1, 76.8, 75.2, 74.2, 73.5, 73.2, 72.3, 68.2, 21.4; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{33}ClNaO_4S$ 619.1686, found 619.1667; $[M + NH_4]^+$ calcd for $C_{36}H_{37}ClNO_4S$ 614.2132, found 614.2132.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**(2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-5-(2-chloro-5-methoxybenzo[*b*]thiophen-3-yl)-3,4-dihydro-2*H*-pyran (3c).** 113 mg, 65% yield; colorless oil; IR (neat $cm^{-1}$) 1069, 734, 696; $[\alpha]_D$ (*c* 0.5, $CHCl_3$) +4.4; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.52 (d, *J* = 8.8 Hz, 1H), 7.39−7.20 (m, 11H), 7.14−7.01 (m, 3H), 6.94 (dd, *J* = 2.4 and 8.8 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 2H), 6.52 (s, 1H), 4.76 (d, *J* = 11.6 Hz, 1H), 4.68 (d, *J* = 11.6 Hz, 1H), 4.60 (s, 2H), 4.46 (bq, *J* = 5.6 and 9.2 Hz, 1H), 4.40 (bd, *J* = 4.4 Hz, 1H), 4.30 (d, *J* = 11.2 Hz, 1H), 4.15 (d, *J* = 11.2 Hz, 1H), 4.04 (bt, *J* = 5.6 Hz, 1H), 3.99 (dd, *J* = 6.0 and 10.6 Hz, 1H), 3.82 (dd, *J* = 3.4 and 10.6 Hz, 1H), 3.66 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ 157.7, 145.6, 140.2, 138.2, 137.8, 137.7, 130.5, 129.7, 129.0, 128.8, 128.4, 128.3, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 122.3, 114.7, 105.9, 105.3, 76.5, 74.6, 74.0, 73.5, 72.9, 72.2, 68.2, 55.3; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{33}ClNaO_5S$ 635.1635, found 635.1656; $[M + NH_4]^+$ calcd for $C_{36}H_{37}ClNO_5S$ 630.2081, found 630.2073.

**(2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-5-(5-(*tert*-butyl)-2-chlorobenzo[*b*]thiophen-3-yl)-3,4-dihydro-2*H*-pyran (3d).** 131 mg, 72% yield; colorless oil; IR (neat $cm^{-1}$) 1653, 1069, 732, 695; $[\alpha]_D$ (*c* 0.5, $CHCl_3$) +6.1; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.59 (d, *J* = 8.8 Hz, 2H), 7.40−7.24 (m, 11H), 7.11−6.98 (m, 3H), 6.77 (d, *J* = 6.4 Hz, 2H), 6.52 (s, 1H), 4.77 (d, *J* = 11.8 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.60 (s, 2H), 4.48 (bq, *J* = 5.6 and 9.2 Hz, 1H), 4.37 (d, *J* = 4.4 Hz, 1H), 4.26 (d, *J* = 11.6 Hz, 1H), 4.11 (d, *J* = 11.6 Hz, 1H), 4.07−3.80 (m, 2H), 3.82 (dd, *J* = 3.6 and 10.8 Hz, 1H), 1.28 (s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ 148.0, 145.4, 139.0, 137.9, 137.8, 134.2, 130.1, 129.5, 128.5, 128.4, 127.9, 127.8, 127.7, 127.6, 127.3, 123.0, 121.2, 119.0, 106.0, 77.2, 76.4, 74.2, 73.8, 73.6, 72.7, 72.0, 68.3, 34.7, 31.5; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{39}H_{39}ClNaO_4S$ 661.2155, found 661.2156; $[M + NH_4]^+$ calcd for $C_{39}H_{43}ClNO_4S$ 656.2601, found 656.2589.

**(2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-5-(2-chloro-7-methylbenzo[*b*]thiophen-3-yl)-3,4-dihydro-2*H*-pyran (3e).** 109 mg, 64% yield; colorless oil; IR (neat $cm^{-1}$) 1651, 1069, 730, 695; $[\alpha]_D$ (*c* 0.5, $CHCl_3$) +15.4; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.47 (d, *J* = 8.0 Hz, 1H), 7.40−7.20 (m, 12H), 7.18−7.01 (m, 3H), 6.78 (d, *J* = 6.4 Hz, 2H), 6.51 (s, 1H), 4.77 (d, *J* = 11.6 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.63−4.57 (m, 2H), 4.47−4.40 (m, 2H), 4.25 (d, *J* = 11.6 Hz, 1H), 4.11 (d, *J* = 11.6 Hz, 1H), 4.04−3.94 (m, 2H), 3.80 (dd, 3.4 and 10.6 Hz, 1H), 2.48 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ 145.6, 139.2, 138.0, 137.9, 137.7, 137.6, 137.4, 137.2, 131.1, 130.6, 128.5, 128.4, 128.0, 127.8, 127.7, 127.6, 127.3, 125.2, 125.1, 120.6, 106.3, 76.8, 74.9, 74.2, 73.5, 73.1, 72.3, 68.2, 20.1; HRMS (ESI-TOF) *m*/*z* $[M + NH_4]^+$ calcd for $C_{36}H_{37}ClNO_4S$ 614.2132, found 614.2094.

**((2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-5-(2-chlorobenzo[*b*]thiophen-3-yl)-3,4-dihydro-2*H*-pyran-2-yl)methyl Acetate (3f).** 94 mg, 68% yield; colorless oil; IR (neat $cm^{-1}$) 1739, 1651, 732, 696; $[\alpha]_D$ (*c* 0.5, $CHCl_3$) +7.0; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.78−7.62 (m, 2H), 7.40−7.26 (m, 7H), 7.15−7.01 (m, 3H), 6.84−6.74 (m, 2H), 6.49 (s, 1H), 4.78 (d, *J* = 11.6 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.63−4.55 (m, 1H), 4.47−4.35 (m, 3H), 4.27 (d, *J* = 11.4 Hz, 1H), 4.12 (d, *J* = 11.4 Hz, 1H), 3.93 (dd, *J* = 4.6 and 5.8 Hz, 1H), 2.10 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ 170.8, 145.2, 137.6, 137.5, 137.0, 129.6, 128.8, 128.6, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 126.1, 124.8, 122.9, 121.7, 106.2, 77.2, 75.2, 74.1, 73.8, 73.0, 72.4, 62.6, 20.9; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{27}ClNaO_5S$ 557.1165, found 557.1178; $[M + NH_4]^+$ calcd for $C_{30}H_{31}ClNO_5S$ 552.1611, found 552.1600.

**(2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-2-((benzyloxy)methyl)-5-(2-bromobenzo[*b*]thiophen-3-yl)-3,4-dihydro-2*H*-pyran (3g).** 109 mg, 61% yield; pale yellow oil; IR (neat $cm^{-1}$) 1652, 1065, 730, 695; $[\alpha]_D$ (*c* 0.5, $CHCl_3$) +4.2; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.69 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.40−7.25 (m, 12H), 7.15−7.01 (m, 3H), 6.74 (d, *J* = 6.8 Hz, 2H), 6.49 (s, 1H), 4.77 (d, *J* = 11.6 Hz, 1H), 4.70−4.57 (m, 3H), 4.48−4.37 (m, 2H), 4.24 (d, *J* = 11.2 Hz, 1H), 4.07 (d, *J* = 11.2 Hz, 1H), 4.03−3.96 (m, 2H), 3.80 (dd, *J* = 3.2 and 10.4 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ 145.6, 139.6, 139.4, 137.7, 132.9, 129.0, 128.5, 128.4, 128.2, 128.0, 127.8, 127.7, 127.6, 127.4, 124.7, 124.6, 123.0, 121.5, 115.7, 107.0, 76.7, 74.9, 74.2, 73.5, 73.1, 72.4, 68.2; HRMS (ESI-TOF) *m*/*z* $[M + NH_4]^+$ calcd for $C_{35}H_{35}BrNO_4S$ 644.1470, found 644.1465.

**((2*R*,3*S*,4*R*)-3,4-Bis(benzyloxy)-5-(2-bromobenzo[*b*]thiophen-3-yl)-3,4-dihydro-2*H*-pyran-2-yl)methyl Acetate (3h).** 99 mg, 60% yield; pale yellow oil; IR (neat $cm^{-1}$) 1739, 1027, 732, 696; $[\alpha]_D$ (*c* 0.5, $CHCl_3$) +1.4; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$ 7.78−7.61 (m, 2H) 7.46−7.21 (m, 7H), 7.11−7.01 (m, 3H), 6.83−6.71 (m, 2H), 6.48 (s, 1H), 4.79 (d, *J* = 11.6 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.61 (dd, *J* = 6.4 and 12.0 Hz, 1H), 4.49−4.34 (m, 3H), 4.25 (d, *J* = 11.2 Hz, 1H), 4.10 (d, *J* = 11.2 Hz, 1H), 3.93 (dd, *J* = 4.6 and 5.8 Hz, 1H), 2.10 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) $\delta$ 170.9, 145.2, 139.7, 137.5, 132.9, 128.8, 128.6, 128.5, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 126.4, 124.9, 123.4, 121.7, 107.2, 77.2, 75.2, 74.2, 73.9, 73.0, 72.5, 62.6, 21.1; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{27}BrNaO_5S$ 601.0660, found 601.0653; $[M + NH_4]^+$ calcd for $C_{30}H_{31}BrNO_5S$ 596.1106, found 596.1099.

## ■ ASSOCIATED CONTENT

### Supporting Information

$^1H$ and $^{13}C\{H\}$ spectra on all new compounds. 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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