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Enantioselective Synthesis of a Furan Lignan (+)-Sylvone

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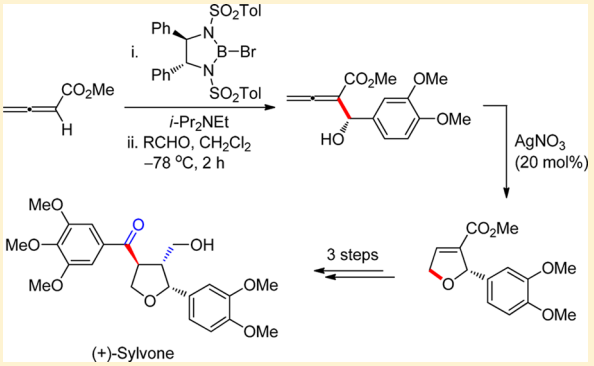
Supporting Information

ABSTRACT: A synthesis of natural tetrahydrofuran lignan (+)-sylvone is achieved starting from methyl allenoate in 5 steps. The synthesis begins from an enantioselective aldol reaction of methyl allenoate with 3,4-dimethoxybenzaldehyde to afford α-addition aldol adduct. Key steps for the synthesis of sylvone include an oxacyclization of the α-hydroxy allenyl adduct followed by a Michael addition of a 1,3-dithiane derivative to establish a sylvone skeleton with suitable stereoselections.



Development of new synthetic protocols for achieving stereoselectivity in the construction of a highly substituted tetrahydrofuran system is a valuable objective owing to the presence of this core unit in many natural products including lignans possessing a diverse array of biological activities.[1] We report herein an efficient enantioselective route to (+)-sylvone, a naturally occurring lignan containing a highly functionalized tetrahydrofuran core.

The lignans are a large family of secondary metabolites widely distributed in plants, representing a vast and rather structurally diverse group of phenylpropane derivatives biochemically produced by oxidative dimerization of two phenylpropanoid units.[2] Within this large family of lignans, a class of tetrahydrofuran derivatives has long been recognized as important natural products in terms of chemistry, biology, nutrition, and medicine.[3] In particular, 2,3,4-trisubstituted tetrahydrofuran lignans are a group of natural products that exhibit a wide range of interesting biological activities which has resulted in them receiving considerable attention over the years. As a consequence, stereoselective construction of these structures, representing a core structure of the furan lignan class, has been an important synthetic target.[4]

Sylvone (**1**) is a class of 2,3,4-trisubstituted tetrahydrofuran lignans isolated from the petrol extracts of seeds derived from *piper sylvaticum*[5] and powdered fruits of *piper logum*,[6] which have been widely used as traditional medicine in Asia. Structurally, sylvone (**1**) contains three contiguous stereogenic centers having a unique substituent arrangement with the 2,3-*cis* stereochemistry, whereas the majority of furan lignans have the substituents arranged with the 2,3-*trans* relationship as shown in Figure 1. The relative stereochemistry of **1** was established by a series of NMR study including NOE experiments[5] and X-ray crystallography.[6] In addition, Rovis and Nasveschuk confirmed the structure of sylvone through synthesis, although its absolute configuration is still not confirmed.[7] Although the biological activity of **1** has not been reported, its 3-epimer (−)-hernone displayed *in vitro* cytotoxic activity against several cell lines.[8]

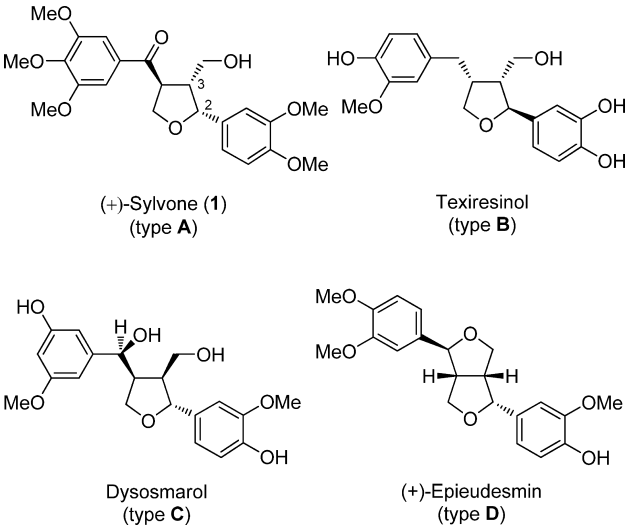


Figure 1. Sylvone (**1**) and related bioactive lignans.

In our continuous efforts to utilize allenyl functionality,[9] we have demonstrated a highly efficient α-addition of methyl allenoate with aldehydes to furnish the aldol adduct **2** with high levels of enantioselectivity.[10] From a synthetic viewpoint, it was envisaged that aldol adduct **2** would serve as a starting material for a sylvone skeleton (type **A**). As illustrated in the synthetic strategy (Scheme 1), our synthesis of a sylvone skeleton type **A** involves three major transformations: an enantioselective

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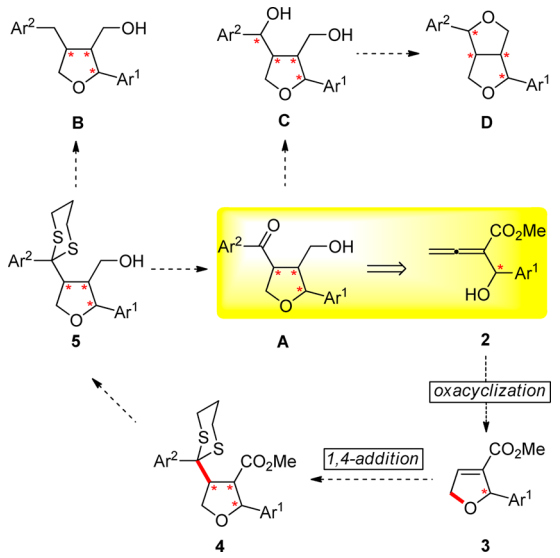
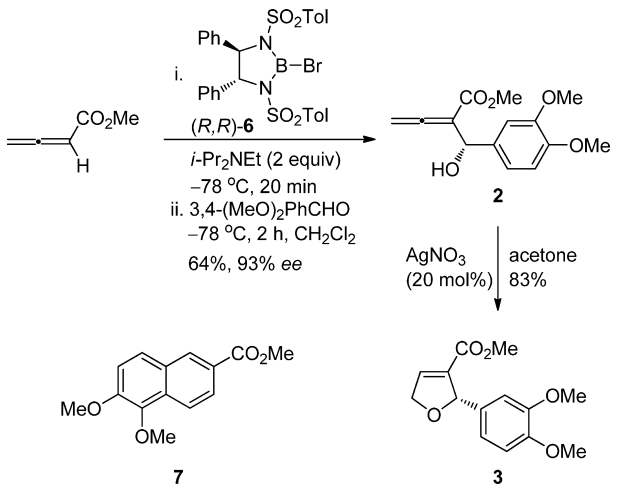
Scheme 1. Synthetic Strategy for the Synthesis of Lignans



synthesis of **2**, an oxacyclization of **2** to afford dihydrofuran **3**, and a Michael addition of a 1,3-dithiane derivative to **3** to afford a crucial intermediate **4**. Moreover, synthetic applications of this protocol can be foreseen to extend to structurally related bioactive lignans such as types **B**, **C**, and **D** from a synthetic intermediate **5** as illustrated in Scheme 1 and Figure 1.[11]

With this issue in mind, our investigations began with methyl allenoate for the synthesis of **2** based on methods previously developed in our laboratory (Scheme 2).[10] To a solution of

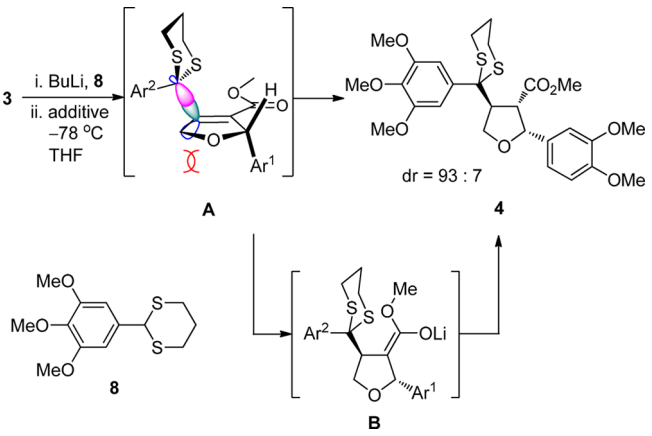
Scheme 2. Synthesis of 3 from Methyl Allenoate



freshly prepared **6** was added a mixture of methyl allenoate and *i*-Pr_2NEt (2 equiv) in CH_2Cl_2 at −78 °C. After 20 min, the resulting mixture was treated with 3,4-dimethoxybenzaldehyde at −78 °C for 2 h in CH_2Cl_2. Neutral aqueous workup using a buffer solution (pH = 7) afforded **2** in 64% yield with 93% *ee*. Initial attempts of an oxacyclization of **2** to **3** using Au(I) or Au(III) catalysts[12] under various conditions turned out to be unproductive, always producing undesired **7** as a major component along with **3** mainly due to a strong electron-donating factor of a 3,4-dimethoxyphenyl moiety.[13a] After screening numerous reaction conditions with Ag(I) and Cu(II) catalysts, we were delighted to find optimal conditions for the formation of **3** in 83% yield as a sole product when the allenyl alcohol **2** was treated with $AgNO_3$ (20 mol %) in acetone at 40 °C for 12 h.[14]

Having achieved a reliable synthesis of the dihydrofuran intermediate **3** through a two-step sequence from methyl allenoate, we proceeded to use this compound for the construction of a 2,3,4-substituted furan framework of sylvone skeleton **4** via a Michael addition (Scheme 3).[15] Although there

Scheme 3. Conjugate Addition of 8 to 3 To Afford 4



have been many examples of Michael addition reactions of furan-2(5*H*)-one derivatives by a 2-aryl-1,3-dithiane with a base in the literature,[15c] cyclic olefins connected to an external ester functionality as a Michael acceptor are not known. Initial attempts for addition of the lithiodithiane Li-**8**, prepared from **8** with *n*-BuLi in THF,[15] to **3** indicated that the conversion to the Michael adduct **4** could not be realized presumably due to a lack of reactivity of Li-**8** (Table 1, entry 1). We subsequently speculated that an activation of the intermediate Li-**8** might require an additive to enhance nucleophilic addition to the α,β-unsaturated ester **3**.[16]

Table 1. Additive Effect for the Addition of 8 to 3[a]

entry	additive	equivalent	*t*, h	yield, %[b]
1	none	–	2	NR[c]
2	HMPA	5	1	23
3	HMPA	5	0.5	63
4	NMP	10	0.5	34
5	DMF	10	0.5	18
6	TMEDA	3	1	<5

[a]After lithiation of **8** with *n*-BuLi at −78 °C in THF, additive was added at −78 °C and then reaction was performed. [b]Refer to isolated and purified yield of **4**. [c]No addition products.

After screening various reaction conditions with coordinating reagents such as HMPA, NMP, DMF, and TMEDA, we found that HMPA was a useful additive in this Michael addition (Table 1). This additive was generally superior to others and was chosen for systematic studies. Initial experiments on the addition of **3** to a solution of Li-**8** and HMPA (5 equiv) at −78 °C in THF for 1 h afforded encouraging but marginal results. Although the Michael adduct **4** was produced during the reaction along with other decomposed impurities, the problem of a low chemical yield (23%) still required resolution (Table 1, entry 2). This low chemical yield was attributed to an instability of a reaction intermediate **B**. Finally, we observed that the

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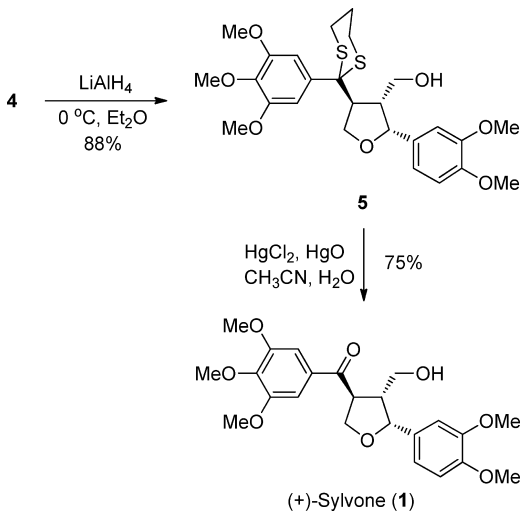
reaction time was a crucial factor for optimal results (Table 1, entry 3). Using the optimized conditions, the reaction was conducted by dropwise addition of **3** (1 equiv) to Li-**8** (1.5 equiv) and HMPA (5 equiv) at −78 °C in THF. After 30 min at −78 °C, the reaction was quenched by the addition of precooled aqueous EtOH via a cannula needle. A neutral aqueous workup procedure gave the Michael adduct **4** as a major component along with another unidentified minor diasteromer in a ratio of 93:7 as judged by the ^{1}H NMR of crude products. Finally, column chromatography on silica gel afforded **4** as a pure form in 63% isolated yield.

From a mechanistic perspective, two major functions for the stereoselectivity in the course of 1,4-addition are immediately discernible: π-facial stereoselectivity and protonation of the enoate **B** in Scheme 3. Stereochemical model **A** in Scheme 3 could illustrate a possible stereochemical route for the π-facial facial selectivity of Li-**8** to **3**. After the conjugate addition, the resulting enolate **B** requires a stereoselective protonation by the addition of aqueous EtOH to give the more sterically favored **4** to establish the 2,3-*cis* relatioship.

With the 2,3,4-trisubstituted furan **4** in hand, all that remained for sylvone **1** was a reduction of the ester functionality and conversion of the thioacetal to a carbonyl group (Scheme 4). Thus, reduction of **4** with $LiAlH_4$ in ether

Scheme 4. Synthesis of (+)-Sylvone (1)



gave **5** in 88% yield. Finally, treatment of **5** with $HgCl_2$ and HgO in CH_3CN and H_2O (4:1) furnished (+)-sylvone (**1**) in 75% yield.[17] All physical data including optical rotation for **1** to prove the absolute configuration were consistent with literature values (observed, $[\alpha]_D^{20}$ +9.76°; Lit.[5] +9.6°).[5,7]

In summary, this paper describes a facile enantioselective synthesis of sylvone (**1**) from methyl allenoate involving the use of several key transformations to construct a 2,3,4-trisubstituted sylvone skeleton with the appropriate three contiguous stereogenic centers: α-addition of an aldehyde of an allenoate, oxacyclization of **2** to **3**, and diastereoselective conjugate addition of a 1,3-dithiane derivative to **3**. This synthetic route may prove to be a general and efficient method for synthesis of related furan lignan natural products and their analogues.

EXPERIMENTAL SECTION

General Methods. Unless otherwise stated, reactions were run in flame-dried glassware under an atmosphere of nitrogen or argon. Solvents were dried by passage through an activated alumina column under argon. And also, dichloromethane was distilled from P_2O_5 prior to use. All liquid reagents purchased from commercial sources were distilled properly prior to use, unless otherwise indicated. Diisopropylethylamine was distilled from CaH_2 prior to use. Hexamethylphosphoramide (HMPA), *N*-methyl-2-pyrrolidone (NMP), dimethylformamide (DMF), and tetramethylethylenediamine (TMEDA) were distilled from CaH_2 prior to use. Purification was conducted by flash column chromatography on silica gel (230−400 mesh), eluting with a mixture of hexanes and ethyl acetate, unless otherwise stated. The reported yields refer to chromatographically purified and isolated products. All reactions were monitored by thin layer chromatography carried out on a silica gel plate (F254) using UV light as a visualizing agent and ethanolic anisaldehyde solution and heat as a developing agent. The reported yields are for chromatographically pure isolated products. ^{1}H NMR spectra were recorded in $CDCl_3$ as a solvent with TMS or residual chloroform as the internal standard (δ 7.26 ppm). ^{13}C NMR spectra were measured in $CDCl_3$ as a solvent and are reportedly related to $CHCl_3$ (δ 77.16 ppm). Optical rotations were measured at ambient temperature (Na line). Elemental Analysis was performed by the Analytical Laboratories. All reported values are within 0.5% of the calculated value. Enantiomeric excesses were determined by HPLC analysis using a chiral column (Chiracel OD-H) in comparison with the sample obtained from (*S*,*S*)-**6**.

(−)-(*S*)-Methyl 2-{(3,4-Dimethoxyphenyl)(hydroxy)methyl}-buta-2,3-dienoate (2). A flame-dried 20 mL Schlenk flask containing (+)-(1*R*,2*R*)-1,2-diphenyl-1,2-bis-*p*-toluenesulfonylamide (0.50 g, 0.96 mmol) was charged with dry CH_2Cl_2 (7 mL) under a nitrogen atmosphere. The resulting mixture was cooled to 0 °C and treated with BBr_3 (freshly prepared 1 M solution in CH_2Cl_2, 1.0 mL, 1.0 mmol). The solution was stirred at 0 °C for 30 min, warmed to 25 °C followed by sitting for an additional 2 h, and then concentrated under vacuum (1 mmHg) through a side neck of the flask connected with a three way regulating valve. Dryness of the vacuum line was maintained with a drying tube containing anhydrous $CaSO_4$ and two traps (NaOH pellets and cold trap at −78 °C). Freshly distilled CH_2Cl_2 (5 mL) was added and evaporated under vauum as mentioned above. Freshly distilled CH_2Cl_2 (3 mL) was added, and the homogeneous solution of (*R*,*R*)-**6** was cooled to −78 °C and treated dropwise with a mixture of methyl allenoate (0.1 g, 1.02 mmol) and *i*-Pr_2NEt (0.35 mL, 0.26 g, 2.01 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was allowed to proceed at −78 °C. After stirring for 20 min at −78 °C, precooled 2,3-dimethoxybenzaldehyde (0.167 g, 1.0 mmol) in CH_2Cl_2 (1 mL) was added via a cannular needle along the wall of the flask while keeping the temperature below −78 °C. The reaction was allowed to proceed for 2 h at −78 °C and then was quenched by addition of an aqueous buffer solution (pH 7, 7 mL) followed by CH_2Cl_2 (ca. 10 mL) to dissolve the white precipitate (bis-sulfonamide). The aqueous layer was extracted with CH_2Cl_2 (ca. 10 mL × 2). The combined organic extracts were washed with brine (1×), dried over anhydrous Na_2SO_4, filtered, evaporated, and taken up in ether (ca. 20 mL). The solution was cooled to 0 °C for 20 min to complete precipitation of (+)-(1*R*,2*R*)-1,2-diphenyl-1,2-bis-*p*-toluenesulfonylamide by filtration through a sintered glass funnel; the filtrate was concentrated under reduced pressure to give the crude product in fairly pure form. Final purification was effected by flash chromatography on SiO_2 (Hexanes/EtOAc = 85:15) to afford **2** (0.16 g, 0.61 mmol, 64%) as a colorless oil: $[\alpha]_D^{20}$ −7.84 (*c* 1.1, $CHCl_3$); IR (neat) 3496, 3061, 2952, 2836, 1963, 1721, 1594, 1518, 1271, 1026, 859, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.36 (d, *J* = 5.4 Hz, 1H), 3.75 (s, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 5.20 (d, *J* = 1.8 Hz, 2H), 5.52−5.54 (m, 1H), 6.80−6.89 (m, 2H), 6.96−6.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.4, 55.8, 71.4, 81.2, 103.8, 109.7, 110.7, 118.6, 118.6, 134.0, 148.5, 148.8, 167.1, 213.0; MS (ESI) *m*/*z* 265.2 (M+1). Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.37; H, 6.33; 93% *ee*. The enantiomeric purity was determined by HPLC analysis (Daicel Chiralcel OD-H,

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Hexane/*i*-PrOH = 9/1, flow rate = 1.2 mL/min, retention time: 7.2 min (major) and 9.0 min (minor)).

(+)-(*R*)-Methyl 2-(3,4-Dimethoxyphenyl)-2,5-dihydrofuran-3-carboxylate (3). A 20 mL flask containing $AgNO_3$ (24 mg, 0.14 mmol) was charged with acetone (5 mL). The reaction flask was wrapped with aluminum foil as protection from light. To this solution allenylcarbinol **2** (0.185 g, 0.7 mmol) in acetone (1 mL) was added at 20 °C. The reaction mixture was allowed to warm to 40 °C. The reaction progress was monitored by TLC. After 12 h at 40 °C, the reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. Purification of the residue by column chromatography (Hexanes/EtOAc = 90:10) afforded **3** (0.154 g, 0.58 mmol, 83%) as a clear liquid: $[\alpha]_D^{20}$ +96.26 (*c* 1.0, $CHCl_3$); IR (neat) 3058, 2956, 2839, 1721, 1640, 1593, 1515, 1261, 1026, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 4.83 (ddd, *J* = 1.8, 3.8, 14.4 Hz, 1H), 4.98 (ddd, *J* = 1.8, 6.1, 14.4 Hz, 1H), 5.86−5.90 (m, 1H), 6.81−6.88 (m, 3H), 6.99−7.05 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.8, 55.9, 55.9, 75.1, 86.8, 110.3, 111.0, 119.6, 133.3, 135.5, 138.6, 149.0, 149.1, 162.9; MS (ESI) *m*/*z* 265.1 (M+1). Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.77; H, 6.21.

2-(3,4,5-Trimethoxyphenyl)-1,3-dithiane (8). An oven-dried 50 mL round-bottom flask was flushed with nitrogen and charged with CH_2Cl_2 (20 mL) and 3,4,5-trimethoxybenzaldehyde (1.0 g, 5.1 mmol). To this solution propane-1,3-dithiol (0.56 mL, 0.57 g, 5.6 mmol) was added at 20 °C. The reaction mixture was allowed to cool to 0 °C using an ice bath, and $BF_3{\cdot}OEt_2$ (0.7 mL, 0.78 g, 5.6 mmol) in CH_2Cl_2 (2 mL) was added over 15 min via syringe with the temperature maintained at 0 °C. The reaction mixture was warmed to 20 °C. After 12 h at 20 °C, the organic layer was washed sequentially with 2.0 M aqueous NaOH (3 × 50 mL) and with brine (1 × 25 mL) and then dried over anhydrous $MgSO_4$. Volatile organics were evaporated under reduced pressure to give a white solid. Final purification was effected by recrystallization from EtOAc to give **8** (0.64 g, 2.23 mmol, 44%) as colorless needles:[14] Mp 87−88 °C; IR (film) 3019, 2967, 1591, 1507, 1459, 1418, 1335, 1238, 1125, 1006, 761, 673 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.93 (dtt, *J* = 13.3, 13.3, 3.0 Hz, 1H), 2.18 (dtt, *J* = 13.3, 3,0, 2.5 Hz, 1H), 2.92 (ddd, *J* = 13.3, 3.0, 2.5 Hz, 2H), 3.06 (ddd, *J* = 13.5, 13.5, 2.5, Hz, 2H), 3.83 (s, 3H), 3.87 (s, 6H), 5.10 (s, 1H), 6.70 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.1, 32.3, 52.0, 56.1, 60.8, 104.7, 134.7, 137.9, 153.4.

(+)-(2*R*,3*S*,4*S*)-Methyl-2-(3,4-dimethoxyphenyl)-4-{2-(3,4,5-trimethoxyphenyl)-1,3-dithian-2-yl}tetrahydrofuran-3-carboxylate (4). A flame-dried 20 mL round-bottom flask with a Teflon-coated magnetic stir bar was capped with a septa, flushed with nitrogen and charged with THF (5 mL) and 1,3-dithiane **8** (0.21 g, 0.73 mmol, 1.5 equiv) at 20 °C. The reaction mixture was cooled to −78 °C. To this solution *n*-BuLi (2.5 M in hexane, 0.3 mL, 0.75 mol, good quality required) was added dropwise, and the reaction proceeded for 1 h at −78 °C. After HMPA (0.64 mL, 0.66 g, 3.65 mmol) in THF (0.5 mL) was added to the reaction vessel, stirring was continued for another 10 min. Compound **3** (0.13 g, 0.49 mmol) in THF (0.5 mL) was added to the resulting reaction mixture. The reaction was allowed to proceed for 30 min at −78 °C. Precooled aqueous EtOH (2 mL) was added via a cannular needle to quench the reaction. Stirring was continued for another 10 min, while the reaction mixture was allowed to warm to room temperature. The product was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with water (3×) and brine (1×) and dried over anhydrous Na_2SO_4. After solid materials were filtered through a sintered glass funnel, the filtrate was concentrated under reduced pressure to give the crude products. The diastereoselectivity (dr = 93:7) was determined by ^1H NMR analysis of the crude products at δ 4.94 ppm (major, d, *J* = 8.9 Hz) and 4.63 ppm (minor, d, *J* = 9.0 Hz). Final purification was effected by SiO_2 chromatography (Hexanes/EtOAc = 90:10) to afford **4** (0.17 g, 0.31 mmol, 63%) as a yellowish oil: $[\alpha]_D^{20}$ +15.48 (*c* 0.7, $CHCl_3$); IR (neat) 3055, 2938, 2909, 2835, 1731, 1584, 1517, 1408, 1266, 1235, 1129, 1027, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.85−2.00 (m, 2H), 2.66−2.80 (m, 4H), 3.05 (s, 3H), 3.35−3.41 (m, 1H), 3.71−3.74 (m, 1H), 3.80−3.85 (m, 15H), 3.90−3.98 (m, 1H), 4.01−4.06 (m, 1H), 4.96 (d, *J* = 8.4 Hz, 1H), 6.76−6.77 (m, 3H), 7.25−7.26 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 27.4, 27.5, 51.6, 52.4, 55.6, 55.8, 55.9, 56.3, 60.9, 61.5, 68.8, 83.6, 106.3, 109.5, 110.4, 119.0, 130.2, 136.2, 137.1, 148.4, 148.5, 153.2, 172.5; MS (ESI) *m*/*z* 551.1 (M+1). Anal. Calcd for $C_{27}H_{34}O_8S_2$: C, 58.89; H, 6.22. Found: C, 59.07; H, 6.28.

(+)-(2*R*,3*R*,4*S*)-2-(3,4-Dimethoxyphenyl)-4-{2-(3,4,5-trimethoxyphenyl)-1,3-dithian-2-yl)tetrahydrofuran-3-yl}-methanol (5). To a stirred suspension of lithium aluminum hydride (30 mg, 2.09 mmol) in dry ether (4 mL) at 0 °C was added a solution of **4** (0.15 g, 0.27 mmol) in ether (1 mL) over a period of 5 min. After stirring for an additional 3 h at 0 °C, the reaction mixture was sequentially treated with water (0.3 mL) and aqueous NaOH solution (15%, 0.5 mL). Stirring was continued vigorously for another 30 min, while the resulting mixture was allowed to warm to room temperature. The resulting suspension was carefully triturated with ether and then dried over Na_2SO_4. The filtrate was concentrated in vacuo to give a crude product in fairly pure form. The crude mixture was purified by flash chromatography (silica gel, EtOAc/hexanes = 85:15) to give the product **5** (124 mg, 0.24 mmol, 88%) as a pale yellow oil: $[\alpha]_D^{20}$ +19.47 (*c* 0.7, $CHCl_3$); IR (neat) 3531, 3056, 2936, 2833, 1584, 1516, 1318, 1267, 1234, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.89−1.98 (m, 2H), 2.68−2.82 (m, 5H), 2.88−2.91 (m, 1H), 3.11−3.16 (m, 2H), 3.21−3.23 (m, 1H), 3.86−3.89 (m, 16H), 3.92−4.03 (m, 1H), 4.79 (d, *J* = 6.3 Hz, 1H), 6.84 (s, 3H), 7.33 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 27.5, 47.9, 54.9, 56.0, 56.1, 56.5, 56.5, 61.0, 62.9, 63.6, 68.1, 82.7, 106.7, 108.8, 111.3, 117.9, 130.6, 136.3, 137.3, 148.4, 149.2, 153.4; MS (ESI) *m*/*z* 523.3 (M+1). Anal. Calcd for $C_{26}H_{34}O_7S_2$: C, 59.75; H, 6.56. Found: C, 59.66; H, 6.71.

(+)-Sylvone (1). To a solution of **5** (0.107 g, 0.20 mmol) in CH_3CN (2 mL) and H_2O (0.5 mL) were added HgO (48 mg, 0.22 mmol) and $HgCl_2$ (120 mg, 0.44 mmol) at 20 °C. The suspension was allowed to proceed for an additional 2 h at 20 °C. The reaction mixture was filtered through a sintered glass funnel with Celite and extracted with ethyl acetate. The organic layers were washed with brine (1×), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to afford sylvone **1** (65 mg, 0.15 mol, 75%) as a pale yellow solid:[5,7] Mp 138−139 °C (recrystallized from EtOAc); $[\alpha]_D^{20}$ +9.76 (*c* 0.7, $CHCl_3$); IR (film) 3462, 3054, 2986, 2939, 2838, 1672, 1586, 1416, 1265, 1129 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (br s, −OH), 2.88−2.90 (m, 1H), 3.42 (d, *J* = 6.3 Hz, 2H), 3.87−3.92 (m, 15H), 4.23−4.31 (m, 2H), 4.42 (t, *J* = 7.5 Hz, 1H), 5.04 (d, *J* = 6 Hz, 1H), 6.86 (s, 3H), 7.41 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.9, 49.8, 56.0, 56.0, 56.4, 61.0, 62.1, 69.2, 81.5, 106.3, 108.8, 111.2, 117.8, 130.5, 131.4, 142.9, 148.3, 149.0, 153.2, 198.6; MS (ESI) *m*/*z* 433.2 (M+1).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01677.

Copies of HPLC chromatogram of **2**, ^1H and ^{13}C NMR spectra for all products (PDF)

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Notes

The authors declare no competing financial interest.

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