JOC The Journal of Organic Chemistry

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Stereospecific Synthesis of Cyclic Sulfite Esters with Sulfur-Centered Chirality via Diastereoselective Strategy and Intramolecular H-Bonding Assistance

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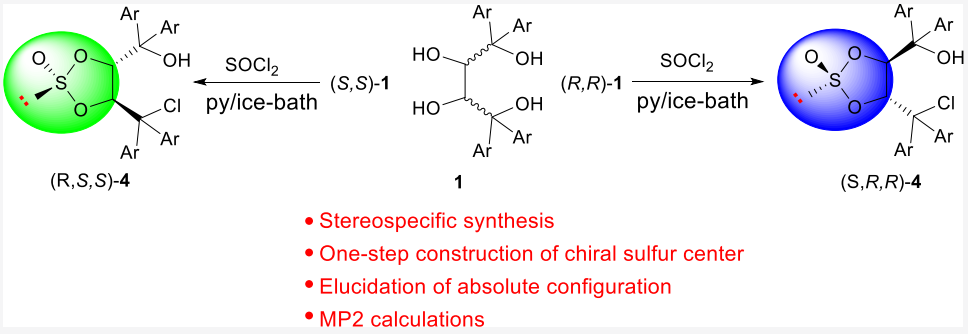


ABSTRACT: Stereospecific synthesis of several cyclic sulfite esters containing three stereogenic centers from enantiopure 1,1,4,4-tetraarylbutanetetraols was achieved. Chiral sulfur centers were constructed stereospecifically via a diastereoselective reaction with the assistance of an intramolecular H-bonding interaction. The absolute configuration of the S atom was elucidated by using the corresponding single-crystal X-ray diffraction analysis of the synthesized monochloride cyclic sulfite esters. Furthermore, a crystallographic evidence of the specific intramolecular $C(sp^3)-H\cdots C_{Ar}$ weak H-bondings was presented, and its dramatic effect on the ^1H NMR spectral properties was revealed. This intriguing behavior was unambiguously rationalized by different shielding effects of the neighboring phenyl rings. Additionally, the theoretical results obtained on the basis of MP2 calculations fully supported the existence of intramolecular hydrogen bonding interactions being responsible for the observed unique chemical and spectral properties.

INTRODUCTION

Chiral sulfur-containing compounds are prevalent in natural products, drugs, and biologically active substances.[1−3] Thus, the synthesis of optically active organosulfur compounds received a considerable research interest so far.[4,5] However, the majority of studies have been focused on preparation of enantiopure and enantioenriched sulfoxides,[6] sulfoximines,[7,8] and other derivatives,[9,10] while chiral sulfite esters have received lesser attention. Nevertheless, cyclic sulfite esters are widely utilized as precursors of cyclic sulfate esters, which are recognized as synthetic equivalents of epoxy compounds.[11,12] Meanwhile, cyclic sulfite esters were shown to undergo ring opening by the attack of nucleophilic reagents that has a practical significance.[13,14] For example, Sudalai group reported the synthesis of chiral three-substituted tetrahydroquinoline derivatives via chiral cyclic sulfite esters, and this method was applied for the preparation of sumanirole maleate and anachelin H chromophore.[15]

As early as in 1952, Herzig and Ehrenstein pointed out that the sulfur atom of sulfite esters could be stereoisomeric because of its tetrahedral geometry.[16] Surprisingly, little attention has been paid to the stereochemical aspects of cyclic sulfites.[17] In 1991, Kagan reported preparation of a mixture of the corresponding diastereomers of chiral cyclic sulfite esters via controlling the addition sequence.[18] Then, García-Granados and co-workers reported preparation and biotransformations of diastereomeric pairs of cyclic sulfite eudesmane derivatives.[19,20] To the best of our knowledge, stereoselective construction of the sulfur chiral center of sulfite esters was not reported. Herein, we report chirogenic formation of the sulfur-center of cyclic sulfite esters via a diastereoselective strategy with the assistance of intramolecular H-bonding, as well as its absolute configuration elucidation.

Received: September 5, 2020

https://dx.doi.org/10.1021/acs.joc.0c02147
J. Org. Chem. XXXX, XXX, XXX−XXX

RESULTS AND DISCUSSION

During our previous studies on the chemistry of chiral 1,1,4,4-tetra-substituted butanetetraols (**1**),[21−25] it was found that (2*R*,3*R*)-1,1,4,4-tetraphenylbutanetetraol (**1a**) was able to undergo a highly regioselective 2,3-cyclosulfitation reaction with thionyl chloride to afford the corresponding cyclic sulfite ester, (4*R*,5*R*)-4,5-bis(diphenyl-hydroxymethyl)-1,3,2-dioxathiolane 2-oxide (**2a**) (Figure 1).[23] Further, addition of thionyl

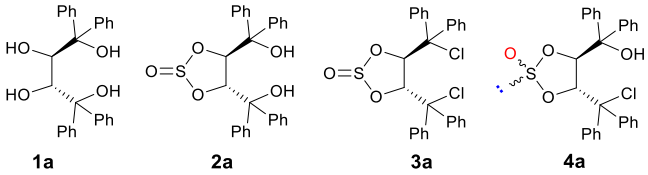
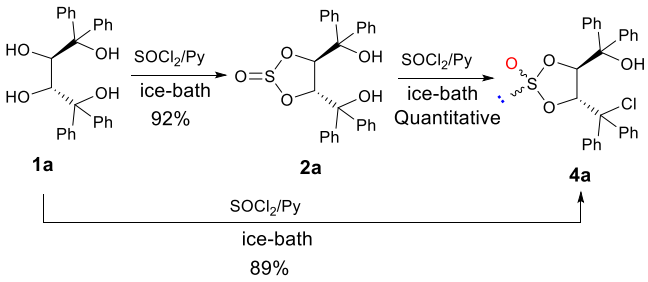


Figure 1. (2*R*,3*R*)-**1a** and its sulfite ester derivatives **2a**−**4a**.

chloride excess resulted in the formation of (4*R*,5*R*)-4,5-bis(diphenylchloro-methyl)-1,3,2-dioxathiolane 2-oxide (**3a**).[22] Based on these results, we envisioned construction of a chiral sulfur center in **4a** via the diastereoselective strategy by controlling the monochlorination reaction of (4*R*,5*R*)-**2a**.

To test this hypothesis, (4*R*,5*R*)-**2a** and varied amount of thionyl chloride were used in the model studies. The optimized conditions were found to include a reaction of (4*R*,5*R*)-**2a** with two equivalents of thionyl chloride in an ice bath to afford **4a** in 89% isolated yield (Scheme 1), while at room temperature, a mixture of **4a** and **3a** was obtained (in a 3:1 ratio).

Scheme 1. Synthesis of Cyclic Sulfite Ester 4a



While the stereochemistry of the sulfur atom was not determined previously, the absolute configuration of both carbons of **4a** is known as *R*,*R*. As mentioned above, according to Kagan and García-Granados,[18−20] a mixture of diastereomers of **4a** would be obtained. However, only one diastereomer was detected based on TLC and ^{1}H NMR analysis. That is to say, the desymmetrization reaction took place in a stereospecific manner to yield one diastereomer exclusively.

To further confirm a chirogenic character of this reaction, several enantiopure 1,1,4,4-tetrasubstituted butanetetraols **1b**−**d** were reacted with thionyl chloride under the optimized conditions. To our delight, all these reactions furnished only one diastereomer of cyclic sulfite esters **4b**−**d** in 62−92% yields, as shown in Scheme 2. This result clearly indicates that the stereospecific desymmetrization reaction of chiral 1,1,4,4-tetraaryl butanetetraols is universal.

To reveal this stereospecific construction process of the chiral sulfur center in sulfite esters, we studied the intramolecular H-bonding interaction of its key intermediate **2a** and product **4a** by using X-ray diffraction analysis. As shown in

Scheme 2. Synthesis of 4b−d from 1b−d

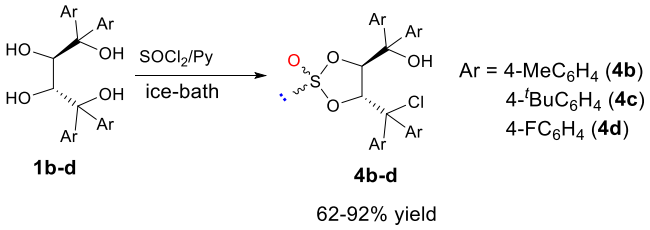


Figure 2 (top), the distances between the proton H3 of the hydroxyl group to sulfinyl O_4 and S_1 are 2.104 and 2.687 Å,

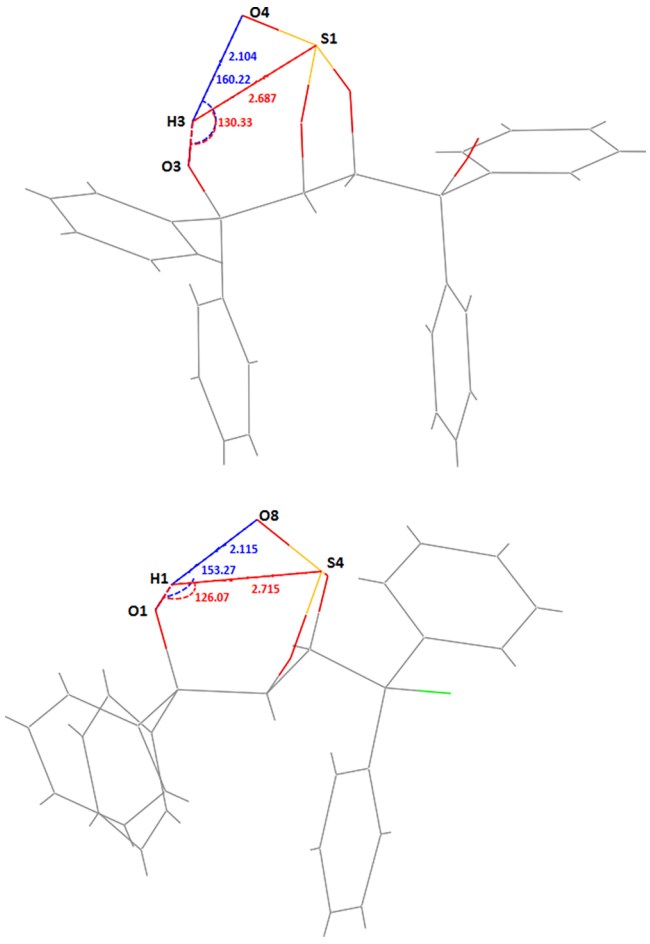


Figure 2. Intramolecular H-bonding in (*R*,*R*)-**2a** (top) and **4a** (bottom) based on the corresponding crystallographic structure.

respectively, with the bond angles for $O_4-H_3-O_3$ and $S_1-H_3-O_3$ being 160.22 and 130.33°, correspondingly. The H-bonding interaction between the sulfinyl group and the hydroxyl group existing in (*R*,*R*)-**2a** forces the sulfinyl group to incline toward the hydroxyl group, which was "protected" by the sulfinyl group, while the other hydroxyl group was readily chlorinated. In fact, this H-bonding interaction is still retained in **4a** even after chlorination (Figure 2 bottom), while the distances between the proton H1 of the hydroxyl group and sulfinyl O_8 and S_4 are 2.115 and 2.715 Å, respectively, with the bond angles for $O_4-H_3-O_3$ and $S_1-H_3-O_3$ being 153.27 and 126.07°, correspondingly. Apparently, this is the reason why the reaction takes place in a stereospecific manner to yield **4a**, exclusively, with the H-bonding between the sulfinyl and

https://dx.doi.org/10.1021/acs.joc.0c02147
J. Org. Chem. XXXX, XXX, XXX−XXX

hydroxyl groups, ensuring the unidirectional approach upon chlorination.

The stereochemistry of both carbons of **4a** at the 4- and 5-positions is *R*,*R*, while the absolute configuration of the S atom at 2-position was determined as *S* based on the corresponding X-ray diffraction analysis (Figure 2, bottom).

Additionally, the X-ray diffraction analysis of **4b** unambiguously confirmed a decisive role of H-bonding in this stereospecific construction of the chiral sulfur center in sulfite esters with the corresponding stereochemistry being also assigned as 2*S*,4*R*,5*R*, as shown in Figure 3.

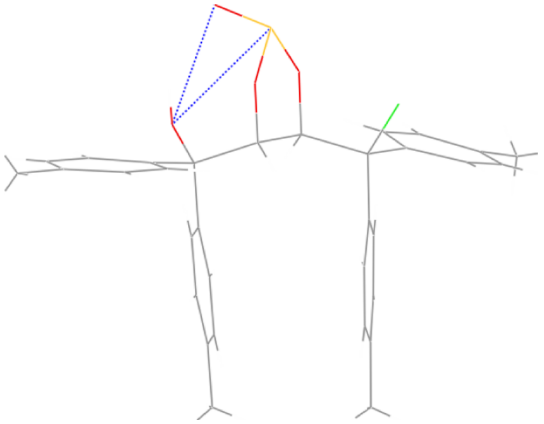
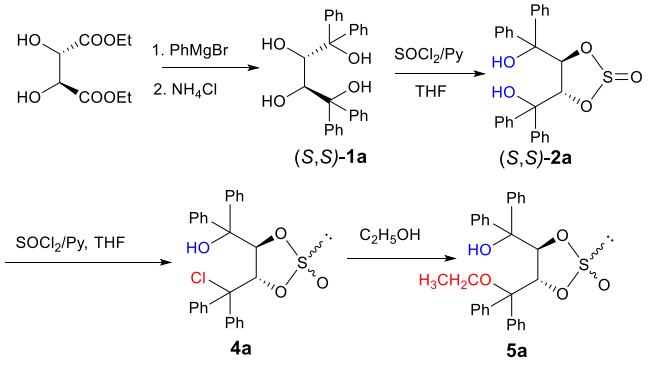


Figure 3. Intramolecular H-bonding in (2*S*,4*R*,5*R*)-**4b** based on the corresponding crystallographic structure.

To further support the stereospecific character of this diastereoselective reaction, diethyl D-tartrate was chosen as a chiral starting material to synthesize (*S*,*S*)-**1a** and (*S*,*S*)-**2a**, correspondingly (Scheme 3). Subsequently, the diastereoselective reaction of (*S*,*S*)-**2a** was carried out to prepare monochlorinated cyclic sulfite ester (2*R*,4*S*,5*S*)-**4a**.

Scheme 3. Synthesis of 5a from Diethyl D-Tartrate



Both the NMR spectrum and the melting point of the product are exactly the same as those of (2*S*,4*R*,5*R*)-**4a**, while their optical rotations have the same values of opposite signs. These results confirmed that the product is an enantiomer of (2*S*,4*R*,5*R*)-**4a**. Unfortunately, a single crystal of (2*R*,4*S*,5*S*)-**4a** for corresponding crystallographic analysis could not be obtained. However, we synthesized its ethoxyl derivative **5a** (Scheme 3), and subsequent X-ray diffraction analysis determined the absolute configuration at the S atom as *R* (Figure 4).

Figure 4. Intramolecular H-bonding in (2*S*,4*R*,5*R*)-**5a** based on the corresponding crystallographic structure.

Thus, the chiral sulfur center in (2*R*,4*S*,5*S*)-**5a** is a result of the reaction of (*S*,*S*)-**2a** and thionyl chloride to yield (2*R*,4*S*,5*S*)-**4a**, while the subsequent nucleophilic reaction with ethanol does not affect the overall stereochemistry.

In addition, the X-ray diffraction analysis of (2*R*,4*S*,5*S*)-**5a** indicated that the intramolecular H-bonding was not affected during the nucleophilic attack of ethanol on (2*R*,4*S*,5*S*)-**4a**. Furthermore, it was shown that the intramolecular H-bonding is stable even in protic polar solvents as evidenced by a single-crystal structure obtained from the ethanol solution.

These results clearly demonstrate that the stereospecific diastereoselective strategy to construct a chiral sulfur center is highly efficient. Insights into the X-ray crystallographic data of (*R*,*R*)-**2a**, (2*S*,4*R*,5*R*)-**4a**, (2*S*,4*R*,5*R*)-**4b**, and (2*R*,4*S*,5*S*)-**5a** revealed that the H-bonding between the sulfinyl and hydroxyl groups plays a decisive role in this stereospecific synthesis.

Besides strong intramolecular H-bonding between the sulfinyl and hydroxyl group, weak intramolecular $C(sp^3)-H\cdots C_{Ar}$ bonding networks were also observed in (2*R*,4*S*,5*S*)-**5a**, which markedly influenced the corresponding ^1H NMR spectral properties. For example, two protons of the CH_2 group ($-OCH_2CH_3$) extraordinary upfield shifted up to 2.73 and 1.95 ppm, as shown in Figure 5. Further, the corresponding HMBC spectrum of (2*R*,4*S*,5*S*)-**5a** unambiguously confirmed the signals' assignments (Figure S23).

It is well known that the proton resonance for the methylene protons in dialkyl ethers generally occurs at about 3.4 ppm. Therefore, these upfield shifts imply that the methylene protons of (2*R*,4*S*,5*S*)-**5a** may be strongly shielded by the neighboring aromatic groups. We rationalize that there are $C(sp^3)-H\cdots C_{Ar}$ weak H bonds,[26−28] which force the corresponding methylene protons to be in close proximity to the phenyl ring (Figure 6). Hence, this structural arrangement is responsible for the observed extraordinary upfield shifts in the corresponding ^1H NMR spectrum.

To confirm our assumption, insights into the crystallographic structure evidenced that there are weak intramolecular $C(sp^3)-H\cdots C_{Ar}$ bonding networks between the two methylene protons of the diphenylethoxymethyl group and aromatic carbons, although a certain contribution of the $C-H\cdots\pi$ interaction is also possible.[29] As shown in Figure 7, the distance from the methylene proton H_{29A} of the diphenylethoxymethyl group to the aromatic carbons C_{17} and C_{18} of the equatorial phenyl plane are 2.703 and 2.838 Å, respectively, with the bond angles for $C_{29}-H_{29A}-C_{17}$ and $C_{29}-H_{29A}-C_{18}$ being 92.92 and 102.24°, correspondingly. In the case of another methylene proton H29B, the distances to the aromatic carbons C23 and C24 of the axial phenyl plane are 2.788 and 2.771 Å, respectively, with the bond angles for $C_{29}-H_{29B}-C_{23A}$ and $C_{29}-H_{29B}-C_{24A}$ being 100.58 and 111.36°, correspond-

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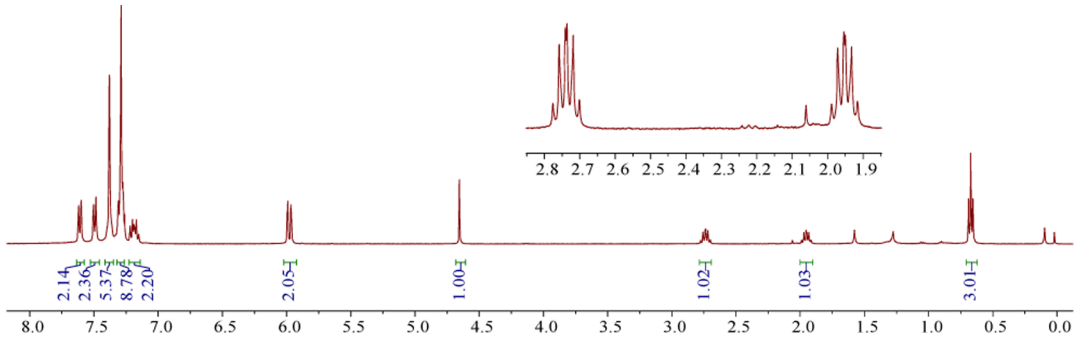

Figure 5. ^{1}H NMR spectrum of (2*R*,4*S*,5*S*)-**5a** and a fragment of the methylene protons resonance of $-OCH_2CH_3$.

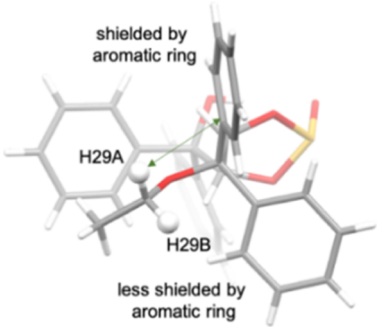

Figure 6. Possible shielding effect caused by the aromatic ring currents for H_{29A} and H_{29B} protons of the $O-CH_2$ group of (2*S*,4*R*,5*R*)-**5a**.

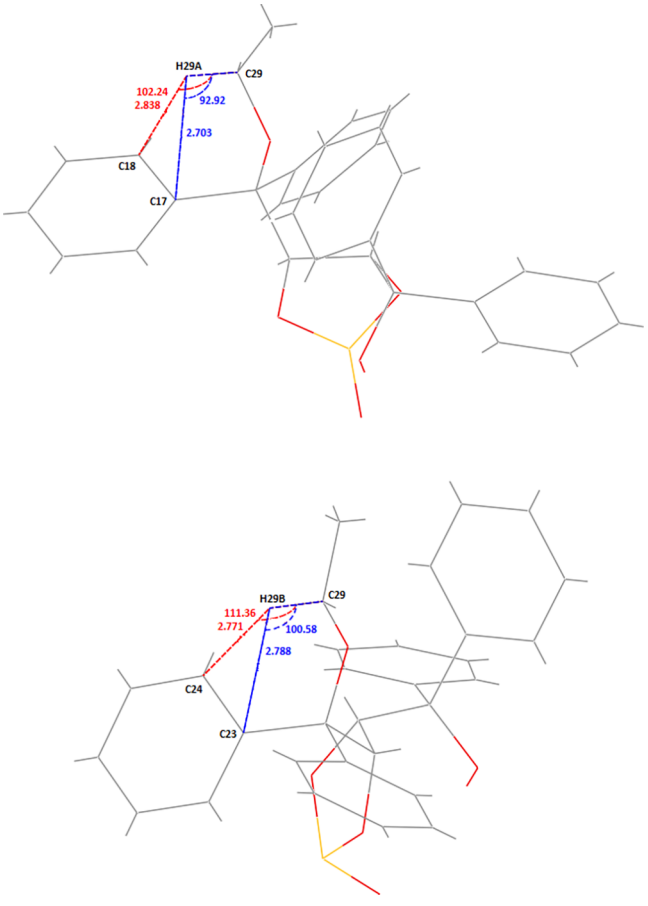

Figure 7. $C(sp^3)-H\cdots C_{Ar}$ weak H bonds in (2*R*,4*S*,5*S*)-**5a**.

ingly. It is clear that the observed $C-H\cdots C_{Ar}$ distances are noticeably shorter than the sum of the corresponding van der Waals radii of C and H atoms (2.90 Å),[30] while the respective angles larger than 90°. These experimental results are in full agreement with the prerequisites of weak H bond formation.[31] Hence, the two methylene protons are in the rigid five- and six-membered cyclic H bond frameworks and the two protons of the CH_2 group in (2*R*,4*S*,5*S*)-**5a** become diastereotopic because of the chirality of the structure, while their corresponding ^{1}H NMR signals are as two sets of multiplets (Figure 5), indicating that both the germinal and vicinal couplings take place in the ethoxy group. Furthermore, the distance between H_{29A} and C_{17} (2.703 Å) is shorter than that between H_{29B} and C_{23}/C_{24} (2.788, 2.771 Å), placing H_{29A} closer to the shielding cone of the aromatic ring and thus producing a stronger shielding effect in the case of H_{29A}. As a result, the H_{29A} and H_{29B} resonances are located at 1.95 and 2.72 ppm, respectively.

Further, to theoretically support the intramolecular strong (between the sulfinyl and hydroxyl groups) and weak hydrogen bonding interactions ($C(sp^3)-H\cdots C_{Ar}$) discussed above, we calculated the corresponding Mulliken charges[32] of (2*R*,4*S*,5*S*)-**5a** by the Møller–Plesset second-order perturbation theory (MP2) with the 6-31G(d,p) basis set,[33,34] in which all geometries (bond lengths, bond angles, and dihedral angles) are taken from the single-crystal X-ray data set. We confirmed no differences in the geometry between the crystal and Gaussian 09 data sets. All data analysis is given in Figure 8, Table 1, and the Supporting Information (Figures S5 and S6 and Tables S5).

All peripheral hydrogen atoms of (2*R*,4*S*,5*S*)-**5a** have positive Mulliken charges ranging of +0.11 and +0.32 (Figure 8 and Tables 1 and S5). Particularly, H_1 attaching to O_1 has an exceptionally high positive Mulliken charge of 0.32. Thus, O_1-H_1 is a very polar group, allowing us to assume that O_1-H_1 plays a key role to cause a strong attractive force with its nearby atoms by through-space (or intramolecular) interactions. For example, the interactions between O_1-H_1 and sulfite groups are highly possible. Actually, the interatomic distances of $H_1\cdots O_4$, $H_1\cdots O_2$, and $H_1\cdots S_1$ are 2.106, 2.621, and 2.706 Å, respectively. These distances are also shorter than the corresponding van der Waals contact radii by 0.61, 0.10, and 0.29 Å, respectively. Multiple $O-H\cdots X$ (X = O or S, see blue or white broken lines in Figure 8) interactions with the sulfite group, supported by the markedly shorten $H_1\cdots O_4$ and $H_1\cdots S_1$ distances and slightly shorten $H_1\cdots O_2$ distance, are responsible for the stereospecific generation of (*R*)-configuration at the S_1 site in (2*R*,4*S*,5*S*)-**5a**. Although the Mulliken charges of H1 and S_1 are commonly positive, the London dispersion force

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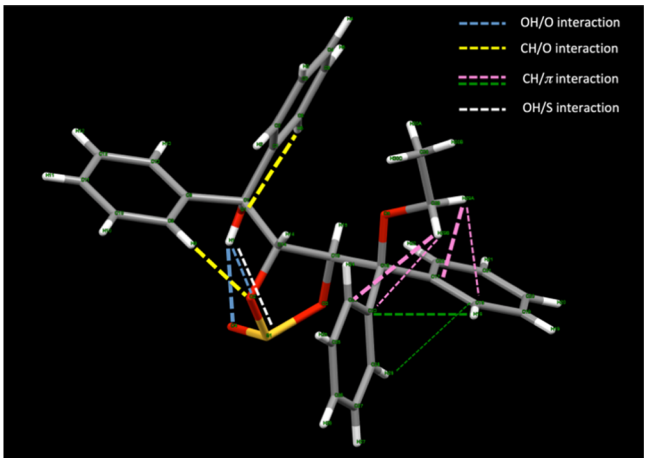

Figure 8. Observed intramolecular H bonds in (2*R*,4*S*,5*S*)-**5a** in the solid state.

may be crucial in this case because of larger 3s, 3p, and 3d orbitals of S_1.

Alternatively, there are two through-space C−H···O hydrogen bonds[35] between the sulfite and phenyl groups and between the O−H and phenyl groups, see yellow broken lines in Figure 8. The interatomic distances between O_2 and H_9 of phenyl and between O_1 and H_6 of phenyl are 2.474 and 2.456 Å, respectively (Table 1). These distances are considerably shorter than the corresponding van der Waals contact radii by 0.25 and 0.26 Å, respectively. These decreased distances indicate a strong C−H···O hydrogen interaction.

More interestingly, there exist two types of the C−H···C interactions in the (2*R*,4*S*,5*S*)-**5a** crystal (Figure 8 and Table 1), see reddish broken lines in Figure 8. Actually, although the ethoxy methylene has two protons (H_{29A} and H_{29B}) attached to C_{29}, a considerably large positive Mulliken charge of H_{29A} (+0.124) efficiently interacts with both negatively charged C_{17} and C_{18} (−0.054 and −0.111, respectively) at one of the two adjacent phenyl groups. Alternatively, a markedly large positive Mulliken charge of H_{29B} (+0.102) interacts with C_{23} and C_{18} charged negatively (−0.115 and −0.112) at another phenyl group. Among these four C−H···C_{Ar} (π) interactions, the C_{29}−H_{29A}···C_{17} interaction was found to be the strongest one, apparently because of the shortest distance reduced to 0.20 Å relative to the van der Waals contact of 2.90 Å. Thus, these four C(sp^3)−H···C_{Ar} (π) interactions are able to fix H_{29A} and H_{29B} in the "frozen" geometry even in a fluidic solution at room temperature, hence resulting in inhibition of its free rotation around the C_{29}−O_5 bond. This situation leads to the unique ^{1}H NMR pattern described above, in which H_{29A} and H_{29B} being geminal protons reveal two doublet proton NMR signals with equal integral intensities. In turn, either H_{29A} or H_{29B} can couple with H_{30A}/H_{30B}/H_{30C}, splitting to quartet signals because of the freely rotatable C_{29}−C_{30} bond. Thus, both H_{29A} and H_{29B} show the corresponding multiplet signals, respectively, that is a plausible explanation for the observed multiplicity of methylene protons in $CDCl_3$.

Besides, there are two other C−H···π interactions between two phenyl groups (Figure 8 and Table 1), see green broken lines in Figure 8. Actually, C_{18}−H_{18} (+0.129) strongly interacts with C_{23} (−0.115), which is the *ipso* carbon of one phenyl group, as supported from 0.25 Å shortening from the corresponding van der Waals contact radii (Table 1). Similarly, C_{28}−H_{28} (+0.129) weakly interacts with C_{18} (−0.111), that is the *ortho* carbon of another phenyl group. Such mutual C−H···π interactions between two phenyl groups should further enforce the C_{29}−H_{29A}···π and C_{29}−H_{29B}···π interactions.

To reveal whether the phenomenon of such a large upfield shift caused by weak H-bonding is rather general or not, several ethoxylation derivatives of chiral cyclic sulfite esters **5b**−**5d** (Figure 9, top) were prepared from **4b**−**4d** according to the same procedure as in the case of the synthesis of (2*R*,4*S*,5*S*)-**5a**. Subsequently, similar effects were observed in the corresponding ^{1}H NMR spectra. As shown in Figure 9 (bottom), all the protons of the CH_2 group (−OCH_2CH_3) of **5b**−**5d** showed two sets of multiplets and upfield shifted. Interestingly, introduction of sterically hindered groups such as ^{t}Bu (**5c**) in the aryl substituent leads to larger upfield shifts of

Table 1. Assignment of Intra-atomic Interactions in the Solid Crystal of (2*R*,4*S*,5*S*)-5a on the Basis of Intra-atomic (Through-Space) Distances and the Corresponding Mulliken Charges[a]

through-space atoms and Mulliken charges (red: negative, blue: positive)	distances (in Å) in crystal (r_{cryst}) and van der Waals contact (r_{vdW}, bracket)[b]	difference between r_{cryst} and r_{vdW} (in Å) (magnitude)
1. O−H···O Interactions (Blue Broken Lines)[c]		
S1−O4(−0.712)···H1(+0.315)-O1	2.106 (2.72)	−0.61 (very strong)
S1−O2(-0.744)···H1(+0.315)-O1	2.621 (2.72)	−0.10 (weak)
2. O−H···S Interactions of Sulfite and Hydroxy Groups (White Broken Lines)[c]		
O1−H1(+0.315)···S1(+1.389)−O4	2.706 (3.00)	−0.29 (strong)
3. C−H···O Interactions[26,36] (Yellow Broken Lines)[c]		
S1−O2(−0.744)···H9(+0.127)-C9(ph)	2.474 (2.72)	−0.25 (strong)
H1−O1(-0.627)···H6(+0.144)-C6 (ph)	2.456 (2.72)	−0.26 (strong)
4. C−H···π Interactions[37] of CH_3−CH_2−O with Two Phenyl Groups (Red Broken Lines)[c]		
C29−H29A(+0.124)···C17(−0.054, ph, *ipso*)	2.703 (2.90)	−0.20 (strong)
C29−H29A(+0.124)···C18(−0.111, ph, *ortho*)	2.841 (2.90)	−0.06 (weak)
C29−H29B(+0.102)···C23(−0.115, ph, *ipso*)	2.789 (2.90)	−0.11 (weak)
C29−H29B(+0.102)···C24(≈0.112, ph, *ortho*)	2.772 (2.90)	−0.13 (weak)
5. C−H···π Interactions[37] between Two Phenyl Groups (Green Broken Lines)[c]		
C18(Ph, *ortho*)−H18(+0.129)···C23(−0.115, Ph, *ipso*)	2.647 (2.90)	−0.25 (strong)
C28(Ph, *ortho*)−H28(+0.129)···C18(−0.111, Ph, *ortho*)	2.844 (2.90)	−0.06 (weak)

[a]All atom's labels were taken from the single-crystal data sets and the Mulliken charges were calculated from Gaussian09 (MP2 functional and 6-31G(d,p) basis sets). [b]Bondi's van der Waals radii, C; 1.70 Å, H; 1.20 Å, O; 1.52 Å, S; 1.80 Å. [c]In Figure 8.

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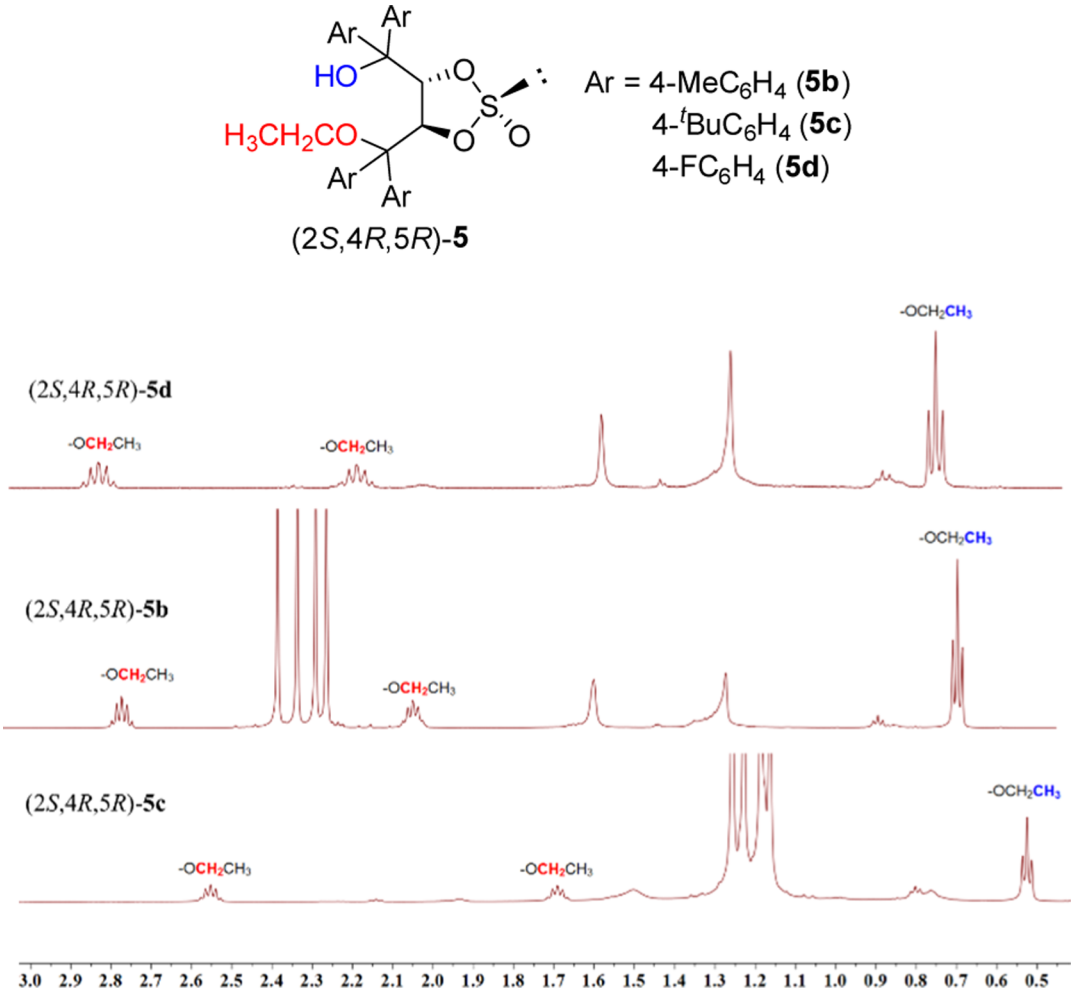

Figure 9. Fragment of methylene proton resonance of $-OCH_2CH_3$ of **5b**–**5d**.

the CH_2 protons (up to 2.56 and 1.69 ppm). However, electron-donating or electron-withdrawing groups, such as methyl (**5b**) and fluoro (**5d**), result in lesser upfield shifts.

CONCLUSIONS

In summary, a stereospecific construction of chiral sulfur centers in several cyclic sulfite esters was realized via the diastereoselective strategy and assistance of intramolecular H-bonding. The mechanism of this chirogenic reaction driven by directional intramolecular H-bonding was established. Further, it was discovered that the intramolecular weak H-bonding of ethoxylation derivatives of chiral cyclic sulfite esters has strong influence on their ^{1}H NMR spectral properties. The corresponding theoretical support of the observed intramolecular hydrogen bonding and experimental stereochemical and spectroscopic results was obtained. This observation can be effectively used to rationalize similar effects in various organic compounds and to establish a rational design of chiral structures with desired stereochemistry.

EXPERIMENTAL SECTION

Materials and Methods. ^{1}H and ^{13}C NMR spectra were obtained on a 600, 400, or 300 MHz NMR spectrometer. The chemical shifts are referenced to signals at 7.26 ppm, using $CDCl_3$ as a solvent. Melting points were determined on a VEB Wagetechnik Rapio PHMK05 instrument and were uncorrected. The single-crystal X-ray diffraction analysis was performed on a Bruker SMART 1 K CCD diffractometer using graphite-monochromated Mo Kα radiation. Diethyl L- and D-tartrate was prepared from L- and D-tartaric acid and ethanol, respectively. THF was freshly distilled after refluxing with Na, while $SOCl_2$ and Py were purchased and used as received. Commercially available starting materials were used without further purification if not specified. **1a**–**1d** are known compounds and prepared according to refs.[21,25]

General Procedure for the Synthesis of 2a. A 25 mL dried round-bottom flask was charged with (*R*,*R*)-**1a** (1.28 g, 3 mmol), pyridine (0.48 mL, 6 mmol), and dried THF (15 mL). The flask was sealed with a rubber septum and stirred in an ice bath for 10 min. Then, $SOCl_2$ (0.3 mL, 3 mmol) was added slowly using a syringe. After complete addition, the mixture was allowed to continuously stir for an additional 2 h in the ice bath. The resultant was treated with water, the organic phase was separated, and the aqueous phase was extracted with Et_2O. The combined extracts were dried over anhydrous Na_2SO_4, concentrated, and cooled. A colorless crystal was isolated, filtered, and dried under vacuum to afford (*R*,*R*)-**2a** with THF, 1.47 g, 90% yield, mp 165–166 °C. $[\alpha]_D^{20}$ +65.8 (*c* 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.03–7.51 (m, 20H, Ar-H), 5.97 (d, *J* = 2.1 Hz, 1H, CH), 5.90 (s, *J* = 2.1 Hz,1H, CH), 4.49 (s, 1H, OH), 3.70 (t, *J* = 6.9 Hz, 4H, CH), 2.37 (s, 1H, OH), 1.83 (t, *J* = 6.3 Hz, 4H, CH). ^{13}C NMR (75 MHz, chloroform-*d*): δ 145.1, 143.3, 141.5, 141.0, 128.7, 128.5, 128.4, 128.0, 127.4, 127.1, 126.7, 126.1, 125.9, 89.7, 87.2, 78.8, 77.7, 68.1, 25.8.

Crystallographic Data for (R,R)-2a.[38] Empirical formula, $C_{32}H_{31}O_6S$, M_w = 543.63, monoclinic, space group, *P*2(1), *a* = 9.5599(9) Å, *b* = 10.5074(9) Å, *c* = 13.9946(12) Å, α = 90°, β = 91.5480 (10)°, γ = 90°, *V* = 1405.2(2) Å^3, *Z* = 2, *F*(000) = 574, *T* =

https://dx.doi.org/10.1021/acs.joc.0c02147
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273(2) K, μ(Mo Kα) = 0.159 mm^{-1}. Of the 8171 measured reflections, 5385 were independent (R(int) = 0.0148). The final refinements converged at R_1 = 0.0361 for $I > 2\sigma(I)$ and wR_2 = 0.0920 for all date. CCDC number: 729972.

(*S*,*S*)-**2a** with THF, 1.50 g, 92% yield, mp 165−167 °C. $[\alpha]_D^{20}$ −65.2 (*c* 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.03−7.52 (m, 20H, Ar-H), 5.97 (d, *J* = 2.1 Hz, 1H, CH), 5.91 (s, *J* = 2.1 Hz,1H, CH), 4.48 (s, 1H, OH), 3.75 (t, *J* = 6.9 Hz, 4H, CH), 2.12 (s, 1H, OH), 1.85 (t, *J* = 6.3 Hz, 4H, CH). ^{13}C NMR (75 MHz, chloroform-*d*): δ 144.7, 142.9, 141.1, 140.5, 128.4, 128.2, 128.0, 126.7, 126.3, 125.7, 125.5, 89.3, 86.7, 78.4, 67.8, 25.4. Calcd for $C_{28}H_{24}O_5S{-}C_4H_8O$: C, 70.70; H, 4.45. Found: C, 70.51; H, 4.42.

General Procedure for the Synthesis of 4. A 25 mL dried round-bottom flask was charged with **1** (2 mmol), pyridine (0.64 mL, 8 mmol), and dried THF (10 mL). The flask was sealed with a rubber septum and stirred in an ice bath for 10 min. Then, $SOCl_2$ (0.4 mL, 4 mmol) was added slowly with a syringe. After complete addition, the mixture was allowed to continuously stir for an additional 2 h in the ice-bath. The resultant was treated with water, the organic phase was separated, and the aqueous phase was extracted with Et_2O. The combined extracts were dried over anhydrous Na_2SO_4, concentrated, and cooled. A colorless crystal was isolated, filtered, and dried under vacuum to afford compound **4**.

*(2S,4R,5R)-4-(Chlorodiphenylmethyl)-5-(hydroxydiphenyl-methyl)-1,3,2-dioxathiolane 2-Oxide ((2S,4R,5R)-**4a**).* 0.87 g, 89% yield, mp 162−164 °C. $[\alpha]_D^{20}$ +54.6 (*c* 0.52, EA). ^{1}H NMR (300 MHz, chloroform-*d*): δ 7.47 (d, *J* = 9.0 Hz, 4H, Ar-H), 7.21−7.34 (m, 8H, Ar-H), 7.05−7.18 (m, 8H, Ar-H), 6.14 (s, 1H, CH), 5.85 (s, 1H, CH), 4.46 (s, 1H, OH). ^{13}C NMR (75 MHz, chloroform-*d*): δ 144.9, 140.5, 128.8, 128.7, 128.5, 128.4, 128.1, 127.8, 127.6, 127.3, 126.8, 126.2, 90.5, 87.1, 78.1.

*Crystallographic Data for (2S,4R,5R)-**4a**.* Empirical formula, $C_{28}H_{23}ClO_4S$; formula weight, M_w = 490.97; volume (V), 4899.2(8) Å^3; Z = 8; crystal system, orthorhombic, space group, $P2(1)2(1)2(1)$; unit cell dimensions (pm), a = 9.6976(9) Å, b = 14.2597(13) Å, c = 35.428(3) Å; α = 90°, β = 90°, γ = 90°; $-11 \le h \le 11$, $-17 \le k \le 16$, $-25 \le l \le 43$; F(000) = 2048; μ = 0.274 mm^{-1}; R(reflections) = 0.0425 (7209); wR_2 (reflections) = 0.1098 (9474); GOF, 1.012; T = 293(2) K; radiation type, Mo Kα. CCDC number: 775757.

*(2R,4S,5S)-4-(Chlorodiphenylmethyl)-5-(hydroxydiphenyl-methyl)-1,3,2-dioxathiolane 2-Oxide ((2R,4S,5S)-**4a**).* 0.87 g, 89% yield, mp 160−162 °C. $[\alpha]_D^{20}$ −53.8 (*c* 0.52, EA). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.46 (dd, *J* = 21.9, 7.7 Hz, 4H, Ar-H), 7.19−7.34 (m, 8H, Ar-H), 7.04−7.15 (m, 8H, Ar-H), 6.14 (s, 1H, CH), 5.84 (s, 1H, CH), 4.45 (s, 1H, OH). ^{13}C NMR (151 MHz, chloroform-*d*): δ 144.7, 140.6, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.6, 127.4, 127.1, 126.6, 126.0, 90.3, 86.9, 77.9. Calcd for $C_{28}H_{23}ClO_4S$: C, 68.49; H, 4.72. Found: C, 68.40; H, 4.69.

*(2S,4R,5R)-4-(Chlorodi-p-tolylmethy)-5-(hydroxydi-p-tolylmethyl)-1,3,2-dioxathiolane 2-Oxide ((2S,4R,5R)-**4b**).* 0.96 g, 88% yield, mp 183−185 °C. $[\alpha]_D^{20}$ +49.7 (*c* 0.5, EA). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.36 (dd, *J* = 12.2, 8.2 Hz, 4H, Ar-H), 7.17−7.05 (m, 6H, Ar-H), 6.98 (d, *J* = 7.9 Hz, 2H, Ar-H), 6.82 (t, *J* = 7.7 Hz, 4H, Ar-H), 6.11 (s, 1H, CH), 5.81 (s, 1H, CH), 4.38 (s, 1H, OH), 2.34 (s, 3H, CH), 2.29 (s, 6H, CH), 2.23 (s, 3H, CH). ^{13}C NMR (101 MHz, chloroform-*d*): δ 142.1, 138.1, 137.6, 136.9, 136.3, 129.0, 128.8, 128.4, 127.4, 126.4, 125.7, 90.3, 87.1, 77.7, 21.0.

*Crystallographic Data for (2S,4R,5R)-**4b**.* Empirical formula, $C_{32}H_{31}ClO_4S$; formula weight, M_w = 547.08; volume (V), 2867.8(7) Å^3; Z = 4; crystal system, orthorhombic; space group, $P2(1)2(1)2(1)$; unit cell dimensions (pm), a = 10.3541(15) Å, b = 12.7989(19) Å, c = 21.640(3) Å; α = 90°, β = 90°, γ = 90°; F(000) = 1152, μ = 0.241 mm^{-1}. $-15 \le h \le 14$, $-18 \le k \le 17$, $-31 \le l \le 31$; R(reflections) = 0.0535 (5677); wR_2 (reflections) = 0.1448 (9329); GOF, 1.016; T = 293(2) K; radiation type, Mo Kα. CCDC: 2020104.

*(2S,4R,5R)-4-(Bis(4-(tert-butyl)phenyl)(hydroxy)methyl)-5-(bis(4-(tert-butyl)phenyl)chloromethyl)-1,3,2-dioxathiolane 2-Oxide ((2S,4R,5R)-**4c**).* 1.31 g, 92% yield, mp 241−243 °C. $[\alpha]_D^{20}$ +36.9 (*c* 0.5, EA). ^{1}H NMR (600 MHz, chloroform-*d*): δ 7.21−7.42 (m, 16H, Ar-H), 6.12 (s, 1H, CH), 5.85 (s, 1H, CH), 4.39 (s, 1H, CH), 1.33 (s, 9H, CH), 1.31 (s, 9H, CH), 1.28 (s, 9H, CH), 1.24 (s, 9H, CH). ^{13}C NMR (151 MHz, chloroform-*d*): δ 151.5, 151.0, 150.1, 149.9, 141.8, 138.0, 128.7, 127.9, 126.2, 125.3, 125.2, 124.9, 90.6, 86.9, 77.8, 34.6, 34.4, 31.4, 31.3. Calcd for $C_{44}H_{55}ClO_4S$: C, 73.87; H, 7.75. Found: C, 73.79; H, 7.70.

*(2S,4R,5R)-4-(Bis(4-fluorophenyl)(hydroxy)methyl)-5-(chlorobis-(4-fluorophenyl)methyl)-1,3,2-dioxathiolane 2-Oxide ((2S,4R,5R)-**4d**).* 0.69 g, 62% yield, mp 90−93 °C. $[\alpha]_D^{20}$ +72 (*c* 0.5, EA). ^{1}H NMR (400 MHz, chloroform-*d*): δ 7.39−7.44 (m, 4H, Ar-H), 7.17 (dd, *J* = 5.4 and 8.0 Hz, 2H, Ar-H), 7.09 (dd, *J* = 5.4 and 8.2 Hz, 2H, Ar-H), 6.98−7.06 (m, 5H, Ar-H), 6.78 (q, *J* = 7.8 Hz, 4H, Ar-H), 6.00 (d, *J* = 2.1 Hz, 1H, CH), 5.70 (d, *J* = 2.1 Hz, 1H, CH), 4.51 (s, 1H, CH). ^{13}C NMR (151 MHz, chloroform-*d*): δ 162.4 (C−F, $^1J_{C-F}$ = 249.8 Hz), 162.2 (C−F, $^1J_{C-F}$ = 249.8 Hz), 162.0 (C−F, $^1J_{C-F}$ = 247.0 Hz), 161.8 (C−F, $^1J_{C-F}$ = 247.8 Hz), 140.1 (C−H, $^4J_{C-F}$ = 3.2 Hz), 137.0 (C−H), 136.4 (C−H, $^4J_{C-F}$ = 3.4 Hz), 135.7 (C−H, $^4J_{C-F}$ = 4.1 Hz), 130.4 (C−H, $^3J_{C-F}$ = 8.3 Hz), 129.5 (C−H, $^3J_{C-F}$ = 8.4 Hz), 128.4 (C−H, $^3J_{C-F}$ = 8.1 Hz), 127.8 (C−H, $^3J_{C-F}$ = 8.3 Hz), 115.5 (C−H, $^2J_{C-F}$ = 19.2 Hz), 115.5 (C−H, $^2J_{C-F}$ = 17.2 Hz), 115.3 (C−H, $^2J_{C-F}$ = 18.9 Hz), 115.3 (C−H, $^2J_{C-F}$ = 17.2 Hz), 90.1 (C−H sp^3), 86.9 (C−H sp^3). Calcd for $C_{28}H_{19}ClF_4O_4S$: C, 59.74; H, 3.40. Found: C, 59.69; H, 3.37.

General Procedure for the Synthesis of 5. A 25 mL dried round-bottom flask was charged with **4** (1 mmol), pyridine (0.1 mL, 1 mmol), and absolute ethanol (6 mL). The mixture was stirred and reflued for 2 h, cooled to room temperature, and concentrated. A colorless crystal was isolated, filtered, and dried under vacuum to afford compound **5**.

*(2R,4S,5S)-4-(Ethoxydiphenylmethyl)-5-(hydroxydiphenyl-methyl)-1,3,2-dioxathiolane 2-Oxide ((2R,4S,5S)-**5a**).* 0.41 g, 81% yield, mp 191−193 °C. $[\alpha]_D^{20}$ −42.9 (*c* 0.5, EA). ^{1}H NMR (600 MHz, chloroform-*d*): δ 7.58 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.46 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.24−7.28 (m, 9H, Ar-H), 7.13−7.19 (m, 2H, Ar-H), 5.96 (s, 1H, CH), 5.94 (s, 1H, CH), 4.62 (s, 1H, OH), 2.71−2.76 (m, 1H, CH), 1.93−1.97 (m, 1H, CH), 0.67 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*): δ 145.2, 141.8, 139.9, 139.4, 129.2, 128.6, 128.2, 128.1, 128.0, 127.8, 127.1, 126.6, 126.5, 90.1, 85.8, 82.7, 77.9, 59.3, 15.5. Calcd for $C_{30}H_{28}O_5S$: C, 71.98; H, 5.64. Found: C, 71.93; H, 5.60.

*Crystallographic Data for (2R,4S,5S)-**5a**.* Empirical formula, $C_{30}H_{28}O_5S$; formula weight, M_w = 500.58; volume (V), 2650.5(5) Å^3; Z = 4; crystal system, orthorhombic; space group, $P2(1)2(1)2(1)$; unit cell dimensions (pm), a = 9.1335(9) Å, b = 14.1693(14) Å, c = 20.480(2) Å; α = 90°, β = 90°, γ = 90°; F(000) = 1056, μ = 0.241 mm^{-1}. $-11 \le h \le 11$, $-16 \le k \le 17$, $-25 \le l \le 25$; F(000), 1152; R(reflections) = 0.0402 (5092); wR_2(reflections) = 0.1128 (7449); GOF, 1.021; T = 296(2) K; radiation type, Mo Kα. CCDC: 942644.

*(2S,4R,5R)-4-(Ethoxydi-p-tolylmethyl)-5-(hydroxydi-p-tolylmethyl)-1,3,2-dioxathiolane 2-Oxide ((2S,4R,5R)-**5b**).* 0.46 g, 83% yield, mp 167−169 °C. $[\alpha]_D^{20}$ +47.2 (*c* 0.5, EA). ^{1}H NMR (600 MHz, chloroform-*d*): δ 7.42 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.36 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.24 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.18−7.11 (m, 2H, Ar-H), 7.09 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.04 (d, *J* = 8.0 Hz, 2H, Ar-H), 5.92 (s, 1H, CH), 5.87 (s, 1H, CH), 4.54 (s, 1H, OH), 2.73−2.78 (m, 1H, CH), 2.37 (s, 3H, CH), 2.32 (s, 3H, CH), 2.28 (s, 3H, CH), 2.25 (s, 3H, CH), 2.01−2.06 (m, 1H, CH), 0.69 (t, *J* = 6.9 Hz, 3H, CH). ^{13}C NMR (151 MHz, chloroform-*d*): δ 137.6, 129.1, 129.0, 128.9, 128.7, 128.6, 128.5, 126.4, 126.3, 90.2, 86.0, 82.4, 77.7, 59.2, 21.2, 21.1, 21.0, 15.5. Calcd for $C_{34}H_{36}O_5S$: C, 73.35; H, 6.52. Found: C, 73.28; H, 6.49.

*(2S,4R,5R)-4-(Bis(4-(tert-butyl)phenyl)(ethoxy)-methyl)-5-(bis(4-(tert-butyl)phenyl)(hydroxy)methyl)-1,3,2-dioxathiolane 2-Oxide ((2S,4R,5R)-**5c**).* 0.63 g, 87% yield, mp 186−187 °C. $[\alpha]_D^{20}$ +33.6 (*c* 0.5, EA). ^{1}H NMR (600 MHz, chloroform-*d*): δ 7.46 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.33 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.14−7.25 (m, 12H, Ar-H), 5.84 (d, *J* = 3.1 Hz, 2H, CH), 4.43 (s, 1H, OH), 2.53−2.58 (m, 1H, CH), 1.67−1.71 (m, 1H, CH), 1.26 (s, 9H, CH), 1.23 (s, 9H, CH), 1.19 (s, 9H, CH), 1.16 (s, 9H, CH), 0.52 (t, *J* = 6.9 Hz, 3H, CH). ^{13}CNMR (101 MHz, chloroform-*d*): δ 150.9, 150.7, 149.6,

https://dx.doi.org/10.1021/acs.joc.0c02147
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142.4, 138.9, 136.9, 136.4, 129.2, 128.3, 126.2, 126.1, 125.4, 125.0, 124.8, 124.4, 90.0, 85.6, 82.1, 77.6, 58.6, 34.5, 34.4, 31.4, 31.3, 15.7. Calcd for $C_{34}H_{36}O_5S$: C, 73.35; H, 6.52. Found: C, 73.28; H, 6.49.

*(2S,4R,5R)-4-(Bis(4-fluorophenyl)(hydroxy)methyl)-5-(ethoxy-bis-(4-fluorophenyl)methyl)-1,3,2-dioxathiolane 2-Oxide ((2S,4R,5R)-**5d**).* 0.43 g, 76% yield, mp 123−125 °C. $[\alpha]_D^{20}$ +52.6 (*c* 0.5, EA). ^{1}H NMR (600 MHz, chloroform-*d*): δ 7.45 (dd, *J* = 8.0, 5.2 Hz, 2H, Ar-H), 7.40 (dd, *J* = 7.7, 5.4 Hz, 2H, Ar-H), 7.31 (dd, *J* = 8.5, 5.4 Hz, 2H, Ar-H), 7.18 (dd, *J* = 8.6, 5.3 Hz, 2H, Ar-H), 7.07 (t, *J* = 8.5 Hz, 2H, Ar-H), 6.98 (t, *J* = 8.7 Hz, 2H, Ar-H), 6.94 (t, *J* = 8.3 Hz, 4H, Ar-H), 5.85 (d, *J* = 1.9 Hz, 1H, CH), 5.77 (d, *J* = 1.9 Hz, 1H, CH), 4.67 (s, 1H, OH), 2.77−2.85 (m, 1H, CH), 2.14−2.21 (m, 1H, CH), 0.75 (t, *J* = 6.9 Hz, 3H, CH). ^{13}C NMR (101 MHz, chloroform-*d*): δ 162.2 (C−F, $^1J_{C-F}$ = 248.7 Hz), 162.3 (C−F, $^1J_{C-F}$ = 258.7 Hz), 161.9 (C−F, $^1J_{C-F}$ = 247.4 Hz), 161.9 (C−F, $^1J_{C-F}$ = 246.9 Hz), 140.4 (C−H, $^4J_{C-F}$ = 3.0 Hz), 137.3 (C−H, $^4J_{C-F}$ = 3.0 Hz), 135.5 (C−H, $^4J_{C-F}$ = 4.0 Hz), 134.8 (C−H, $^4J_{C-F}$ = 4.0 Hz), 130.6 (C−H, $^3J_{C-F}$ = 8.0 Hz), 130.3 (C−H, $^3J_{C-F}$ = 8.0 Hz), 128.4 (C−H, $^3J_{C-F}$ = 8.0 Hz), 128.1 (C−H, $^3J_{C-F}$ = 8.0 Hz), 115.4 (C−H, $^2J_{C-F}$ = 21.8 Hz), 115.2 (C−H, $^2J_{C-F}$ = 21.5 Hz), 115.2 (C−H, $^2J_{C-F}$ = 21.5 Hz), 115.0 (C−H, $^2J_{C-F}$ = 21.3 Hz), 89.9 (C−H sp^3), 85.9 (C−H sp^3), 82.2 (C−H sp^3), 77.2 (C−H sp^3), 59.8 (C−H sp^3), 29.7 (C−H sp^3), 15.4 (C−H sp^3). Calcd for $C_{30}H_{24}F_4O_5S$: C, 62.93; H, 4.23. Found: C, 62.89; H, 4.20.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02147.

^{1}H NMR and ^{13}C NMR spectra for all compounds CIF files for (*R*,*R*)-**2a**, (2*S*,4*R*,5*R*)-**4a**, (2*S*,4*R*,5*R*)-**4b**, (2*R*,4*S*,5*S*)-**5a** (PDF)

Accession Codes

CCDC 2020104, 775757, and 942644 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Nature Science Foundation of China (no. 21302233), the Nature Science Foundation of Hubei Province of China (no. 2012FFB07410), the Fundamental Research Funds for the Central Universities, and the South-Central University for Nationalities (CZY20016) for financial support. J.A. acknowledges funding from the ERDF Grant CoE TK134.

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https://dx.doi.org/10.1021/acs.joc.0c02147
J. Org. Chem. XXXX, XXX, XXX−XXX