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Stereoselective Synthesis and Conformational Analysis of Aromatic *C*-Thionucleosides

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ABSTRACT: *Tetrahydrothiophene derivatives* **2a–2d**, *which are useful intermediates in the synthesis of C-thionucleosides, were obtained by a* tandem *strategy that involves the base-catalyzed conjugate addition of ethyl 2-mercaptoacetate to* trans*-cinnamaldehyde followed by cyclization. The solvent and the nature of the amine used as Lewis base influence the stereoselectivity of the reaction. The reduction of each isolated derivative* **2a–2d** *was performed with* $LiAlH_4$ *to afford C-thionucleosides* **3a–3d**. *The configuration and conformation of each diastereomer* **2a–2d** *and* **3a–3d** *was assigned by means of the analysis of vicinal proton–proton coupling constants. The X-ray structure of* **2d, 3a**, *and* **3b** *confirmed the configuration assigned to each isomeric tetrahydrothiophenes.* © 2006 Wiley Periodicals, Inc. Heteroatom Chem 17:289–298, 2006; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20205

INTRODUCTION

4-Thio-pentafuranosides are interesting compounds from a synthetic point of view because the five-membered ring has resemblance with sugar modified nucleoside analogs presenting antiviral and/or antitumor properties [1–3]. For example, the (*E*)-5-(2-bromovinyl)-4′-thio-2′-deoxyuridine (**I**) is active against some herpes viruses and the 4′-thio-5-fluorouridine (**II**) is active in leukemia L210 infected cells (Fig. 1). On the other hand, *C*-nucleosides isolated from natural sources such as compound **III** in Fig. 1 are relevant because of their potential antiviral activity [4].

Although thionucleosides have recently been obtained through the coupling of 4-thiopentafuranosides with pyrimidine or purine nucleobases [5–7], the synthesis of thionucleosides normally involves several steps. In most of these cases, the key step is the formation of the five-membered ring. Some of the common strategies are shown in Scheme 1. In routes 1 and 2, the 4-thio-pentafuranose ring is formed by contraction [8,9] or cyclization [10,11], respectively, of a carbohydrate that contains at least one thio-substituent. On the other hand, in routes 3 and 4, the 4-thio-pentafuranose ring is obtained via cyclization of noncarbohydrate-based intermediates [12–14].

In 1992, Robert et al. [15] reported the synthesis of tetrahydrothiophene derivatives by means of a base-catalyzed Michael addition-cyclization strategy from chalcones and ethyl 2-mercaptoacetate (Scheme 2).

In this work, we use a two-step/one-pot *tandem* reaction to synthesize the diastereomeric ethyl 3-hydroxy-5-phenyl-tetrahydrothiophene-2-carboxylates **2** as precursors of isomeric *C*-thionucleosides

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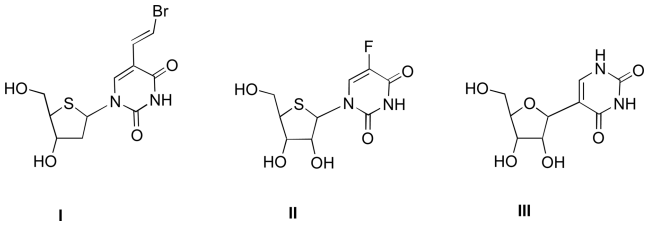


I II III

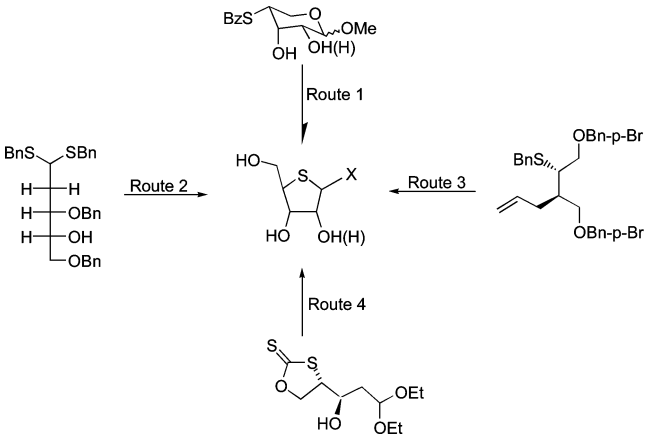
FIGURE 1 Antiviral thionucleosides.

3 (Scheme 3). The stereoselectivity observed in the cyclization step in various solvents and in the presence of several amines, as well as the characterization and conformation of **2a–2d**, is reported in this work. The X-ray structure of the tetrahydrothiophene **2d** and *C*-thionucleosides **3a** and **3b** confirmed the assigned configuration.

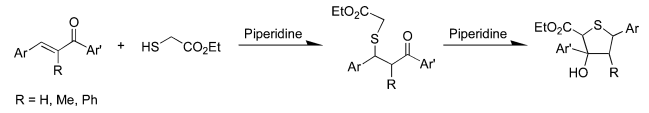
RESULTS AND DISCUSSION

Stereoselective Synthesis

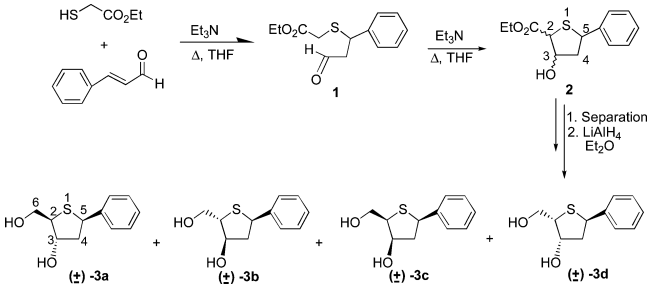
1,4-Adduct (**1**), which is a key intermediate in the reaction, was not isolated. It is worthy of note that *syn* or *anti* attack of the thioanion on the conjugate system cannot be distinguished because the product is obtained as a racemic mixture. Thus, the subsequent cyclization generates a mixture of four diastereomers, each of them was obtained as a racemic mixture, as indicated in Scheme 4. Taking into consideration that during ring closure, the bond between C(2) and C(3) of the diastereomeric products **2** is formed; the approach *lk* of the enolate to the aldehyde [C2(*Si*)/C3(*Si*)] or [C2(*Re*)/C3(*Re*)] gives rise to the racemic products **2a** (5*R*,3*S*,2*S*)/(5*S*,3*R*,2*R*) and **2b** (5*R*,3*R*,2*R*)/(5*S*,3*S*,2*S*), respectively. By contrast, the approach *ul* [C2(*Si*)/C3(*Re*)] or [C2(*Re*)/C3(*Si*)] affords the racemic products **2c** (5*R*,3*R*,2*S*)/(5*S*,3*S*,2*R*) and **2d** (5*R*,3*S*,2*R*)/(5*S*,3*R*,2*S*).



SCHEME 1



SCHEME 2



SCHEME 3

The ratios obtained for each diastereomer were calculated as the raw product and are summarized in Table 1 (the stereochemistry was assigned as indicated below). The stereoselectivity of the reaction was analyzed in different solvents and in the presence of various amines as Lewis bases (Table 1). We observed that in the reactions promoted by TEA, the percentage of product **2d** increases in the solvent with the highest dielectric constant (THF). The

TABLE 1 Diastereoselectivity in the *Tandem* Formation of Ethyl 3-hydroxy-5-phenyl-tetrahydrothiophene-2-carboxylates (**2a–2d**)[a]

Lewis Base (Solvent)	**2a** *(%)*	**2b** *(%)*	**2c** *(%)*	**2d** *(%)*
TEA[b] (THF)	12	18	22	48
TEA (CH_2Cl_2)	21	27	24	28
TEA (Benzene)	20	22	22	36
DMDA[c] (Benzene)	8	11	25	56
DCHA[d] (Benzene)	13	27	34	26
DIPA[e] (Benzene)	7	24	48	21

[a]The percentages were calculated by the area ratio of the proton NMR signals (H_4 and/or H_2) of each diastereomer in the raw material after 24 h of reflux. For DCHA and DIPA, 10–15% of the starting *trans*-cinnamaldehyde was left over.
[b]TEA (triethylamine).
[c]DMDA (*N*,*N*-dimethyldodecylamine).
[d]DCHA (*N*,*N*-dicyclohexylamine).
[e]DIPA (*N*,*N*-diisopropylamine).

fact that the ratio of the products **2a–2d** observed at 24 h (Table 1) remains constant after 48 h or 72 h suggests that this reaction proceeds under thermodynamic control. The product **2d** was the major product with the more congested tertiary amine (DMDA), using benzene as the solvent. With secondary amines DCHA and DIPA, isomer **2c** was preferred. The product **2a**, which has the configuration of the natural nucleosides, was formed to a lesser extent in all cases. The products **2a–2d** were purified by column chromatography as indicated in the experimental part. Isolated yields are in the range of 11–45% of each diastereomer, considering that the four diastereomers are formed in the reaction, and that the percentage of each diastereomer varies with the conditions of the reaction and the Lewis base (Table 1). The reduction of the tetrahydrothiophenes **2a–2d** was performed with $LiAlH_4$, as shown in Scheme 3.

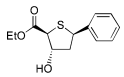
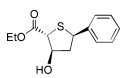
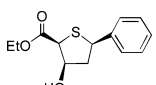
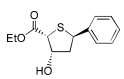
Configuration and Conformation

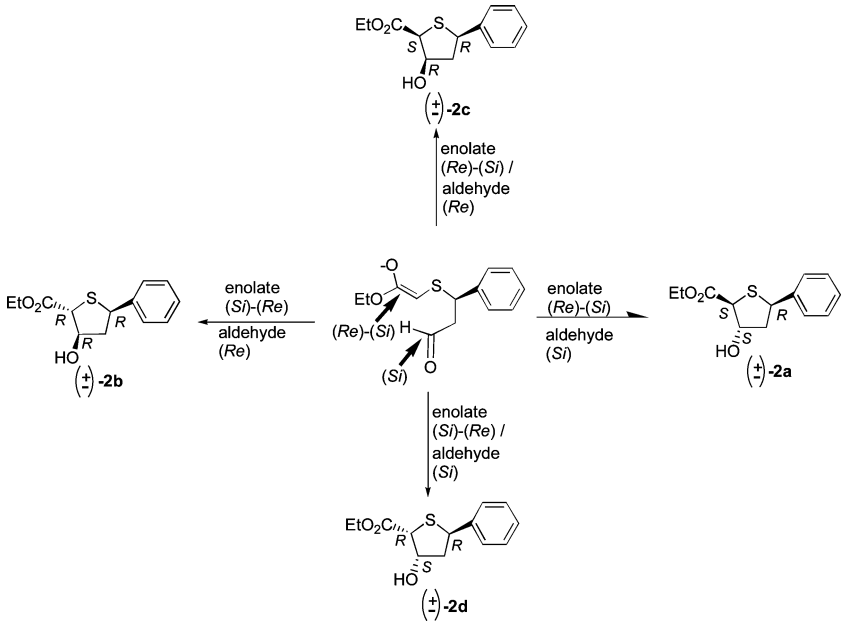
The ^1H NMR signals for the four diastereomers **2** are shown in Table 2. The proton at C(5) is at around 4.8–5.0 ppm for diastereomers **2a** and **2d**, where the secondary alcohol at C(3) is *cis* to C(5)-H. On the other hand, in diastereomers **2b** and **2c**, C(5)-H appears around 4.5–4.6 ppm; this proton is *trans* to the hydroxy group at C(3). Due to the *cis* stereochemistry of the phenyl group at C(5) with the proton C(4)-H_a, this proton is upfield shifted with respect to C(4)-H_b for isomers **2b** and **2d**. However, this effect is counteracted by the ester at C(2), which is in *cis* configuration to C(4)-H_a, for the isomers **2a** and **2c**, provoking the chemical shifts of C(4)-H_a and C(4)-H_b for **2a** and **2c** to be very close to one another.

Vicinal $^3J_{HH}$ coupling constants were obtained by first-order analysis of proton NMR spectra and homonuclear decoupling experiments (Table 2). The protons of the methylene group at C(4) are coupled to the methine protons at C(5) and C(3) with coupling constants that characterize their *gauche* (2.6–6.6 Hz) or *anti* (7.3–10.6 Hz) relationship. The $^3J_{4(a\,or\,b)-5}$ and $^3J_{4(a\,or\,b)-3}$ values found for each diastereomers (Table 2) allowed the relative configuration of these three centers to be assigned. The coupling constant $^3J_{3-2}$ confirmed the configuration at C_2. The "in situ" reaction with trichloroacetyl isocyanate (TAI) [16] of the secondary alcohol at C_3 for **2c** and **2d** did not provoke change in the chemical shift of C(2)-H; however, high-frequency shifts of 0.14 and 0.27 ppm were observed upon addition of TAI to **2b** and to **2a**, respectively. These observations confirm the *trans* nature of C(2)-H and C(3)-OH in **2c** and **2d** and the *cis* nature of the same groups in **2b** and **2a** isomers.

The conformation of the five-membered ring, for each diastereomer, was obtained by the torsion angles calculated with the vicinal coupling constants through the Altona software [17] (Table 3). The torsion angles $\omega_{H2\text{-}C2\text{-}C3\text{-}H3}$, $\omega_{H3\text{-}C3\text{-}C4\text{-}H4(a\,or\,b)}$, and

TABLE 2 Selected ^1H Chemical Shifts (δ, in ppm) and Backbone Coupling Constants (J, in Hz) for Tetrahydrothiophenes **2a–2d** in $CDCl_3$

	Chemical Shifts (δ)				
Compound	*C5-H*	*C4-H_a* ($^3J_{4a\text{-}5}$) ($^3J_{4a\text{-}3}$)	*C4-H_b* ($^3J_{4b\text{-}5}$) ($^3J_{4b\text{-}3}$)	*C3-H*	*C2-H* ($^3J_{2\text{-}3}$)
 **2a**	4.82	2.47 (8.3) (1.0)	2.50 (8.9) (1.6)	4.85	3.97 (2.0)
 **2b**	4.63	2.28 (10.2) (9.6)	2.71 (5.9) (5.3)	4.75	4.08 (7.3)
 **2c**	4.46	2.65 (10.6) (10.6)	2.53 (6.6) (5.9)	4.53	3.99 (6.6)
 **2d**	5.01	2.06 (10.6) (3.3)	2.60 (5.9) (2.6)	4.84	4.39 (4.0)

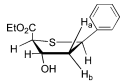
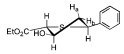
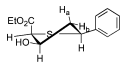
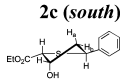


SCHEME 4

$\omega_{H5\text{-}C5\text{-}C4\text{-}H4(a\,or\,b)}$ are indicative of the *gauche* or *anti* H—H vicinal relationship in *twist* conformations. If these angles are close to zero or 120°, respectively, the conformation of the ring tends to be an *envelope* (*E*). In *twist* (*T*) conformations, the notation *north* or *south* was assigned according to the relation of C(3) with the substituent at C(5) [18,19]. For *north* conformation C(3) is *endo* or *syn* to the phenyl at C(5); for *south* C(3) is *exo* or *anti* to the phenyl at C(5). The values found for the torsion angles that are summarized in Table 3 indicate that in solution the five-membered ring is in a preferred *twist–south* conformation for isomers **2b–2d** and in a "quasi" *envelope* conformation for **2a**.

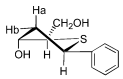
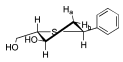
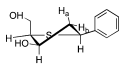
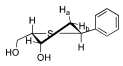
A similar criterion was used to analyze the solution conformation of compounds **3a–3d**. The proton chemical shifts and vicinal coupling obtained by homonuclear decoupling experiments are shown in Table 4. Here again it was observed that with the exception of **3a**, the five-membered ring adopted a *twist–south* conformation for all the compounds. The conformation for isomer **3a** is also twist, however the puckering is between C(5) and C(4) instead of C(3) and C(4) as normally observed. The

TABLE 3 Torsion Angles (ω, deg)[a] for Tetrahydrothiophenes **2a–2d** in $CDCl_3$

Compound	$\omega_{H2\text{-}C2\text{-}C3\text{-}H3}$	$\omega_{H3\text{-}C3\text{-}C4\text{-}H4a}$	$\omega_{H3\text{-}C3\text{-}C4\text{-}H4b}$	$\omega_{H5\text{-}C5\text{-}C4\text{-}H4a}$	$\omega_{H5\text{-}C5\text{-}C4\text{-}H4b}$
					
2a (E)	− 70	− 70	80	142	24
					
2b (*south*)	147	− 159	− 52	153	43
					
2c (*south*)	39	− 167	− 48	156	39
					
2d (*south*)	43	− 49	70	156	43

[a]Calculated by $^3J_{HH}$ coupling constants of Table 2, according to [17].

TABLE 4 Selected ^{1}H Chemical Shifts (δ, in ppm) and Backbone Coupling Constants (J, in Hz) for *C*-Thionucleosides **3a–3d** in Acetone-d_6[a]

	Chemical Shifts (δ)						
Compound	*C*5-*H*	*C*4-H_a ($^3J_{4a\text{-}5}$) ($^3J_{4a\text{-}3}$)	*C*4-H_b ($^3J_{4b\text{-}5}$) ($^3J_{4b\text{-}3}$)	*C*3-*H*	*C*2-*H* ($^3J_{2\text{-}3}$)	*C*6-H_a ($^3J_{6a\text{-}2}$)	*C*6-H_b $^3J_{6b\text{-}2}$)
	4.77	2.08 (11.2) (3.3)	2.30 (5.3) (2.0)	4.64	3.45 (1.3)	3.62 (6.6)	3.64 (6.6)
3a							
	4.51	2.16 (11.2) (9.9)	2.58 (5.9) (5.3)	4.24	3.58 (7.9)	3.89 (5.3)	3.68 (6.6)
3b (*south*, γ^+)							
	4.40	2.26 (10.6) (10.9)	2.52 (5.9) (5.6)	4.64	3.58 (5.3)	4.06 (8.6)	3.78 (4.0)
3c (*south*, γ^+)							
	4.81	2.10 (10.6) (3.3)	2.41 (5.3) (2.3)	4.72	3.72 (b)	3.95 (6.6)	3.95 (6.6)
3d (*south*, γ^+)							

[a]The data reported for isomer **3c** are in $CDCl_3$.
[b]Not determined.

TABLE 5 X-ray Crystal Data for Compounds **2d, 3a**, and **3b**[a]

	2d	**3a**	**3b**
Formula	$C_{13}H_{16}O_3S$	$C_{11}H_{14}O_2S$	$C_{11}H_{14}O_2S$
F_w	252.33	210.29	210.29
Crystal system	Monoclinic *P*	Orthorombic	Monoclinic *P*
Crystal size (mm)	$0.15 \times 0.33 \times 0.45$	$0.15 \times 0.33 \times 0.33$	$0.24 \times 0.36 \times 0.42$
Space group	$P2_1/c$	$Pb2_1a$	$P2_1/a$
Radiation	Mo Kα	Mo Kα	Mo Kα
Wavelength (Å)	0.71069	0.71069	0.71069
a (Å)	9.7732(7)	7.390(1)	9.228(1)
b (Å)	4.9103(4)	9.924(1)	5.5158(8)
c (Å)	27.078(1)	13.9012(8)	20.620(3)
α (deg.)	90.00	90.00	90.00
β (deg.)	95.178(5)	90.00	92.941(9)
γ (deg.)	90.00	90.00	90.00
V (Å^3)	1294.2(2)	1019.4(2)	1048.2(2)
Z	4	4	4
$2\theta_{max}$ (deg.)	52	52	52
d_{calc} (Mg m^{-3})	1.295	1.370	1.333
Absorption coefficient (mm^{-1})	0.244	0.287	0.279
No. of reflections collected	2487	1109	2032
No. of independent reflections	2232	1041	1819
No. of observed reflections	1633	979	1407
$R = \Sigma \|\|F_o\| - \|F_c\|\|)/\Sigma\|F_o\|$	0.0535	0.0250	0.0417
$R_w = [\Sigma_w(\|F_o\| - \|F_c\|)^2/\Sigma_w F_o^2]^{1/2}$	0.0324	0.0298	0.0343
Goodness of fit s	1.33	1.15	1.06
Maximum Δ/σ	0.0003	0.0003	0.0003
$\Delta\rho_{max}$ (e/Å^3)	0.45	0.18	0.30
$\Delta\rho_{min}$ (e/Å^3)	−0.24	−0.17	−0.32

[a]Standard deviations are in parentheses.

conformation around the exocyclic hydroxy group at C(6) was obtained from the torsional angles $\omega_{H6a\text{-}C6\text{-}C2\text{-}H2}$ and $\omega_{H6b\text{-}C6\text{-}C2\text{-}H2}$. The notation γ^+ is given for the rotamer where the bond C(6)—O bond is synclinal to the bond C(2)—C(3), with the OH situated above the ring; γ^t is given when the OH at C(6) is *trans* to the bond C(2)—C(3) and γ^- is given for the rotamer where the OH at C(6) is synclinal to the bond C(2)—C(3), with the OH situated outside the ring.

X-Ray Analysis

The crystallographic data and ORTEP structures of **2d, 3a**, and **3b** are shown in Table 5 and Figs. 2–4 correspondingly. In support to the assigned configuration, the X-ray structure of **2d** shows the *trans–tran*s relationship between the substituents at C(5)—C(3) and C(5)—C(2), respectively. The five-membered ring is in *twist–south* conformation as in solution. On the other hand, the ORTEP structure of **3a** and **3b** confirms the configuration assigned by NMR to these isomers, being the relationship between the substituents at C(5)—C(3) and C(5)—C(2) *trans–cis* for **3a** and *cis–trans* for **3b**. The conformation of the tetrahydrothiophene ring is almost an envelope for **3a** and *twist–south* for **3b**. The conformation of the exocyclic CH_2OH group is γ^- for **3a** and γ^+ with the OH at C(6) situated above the ring for **3b**.

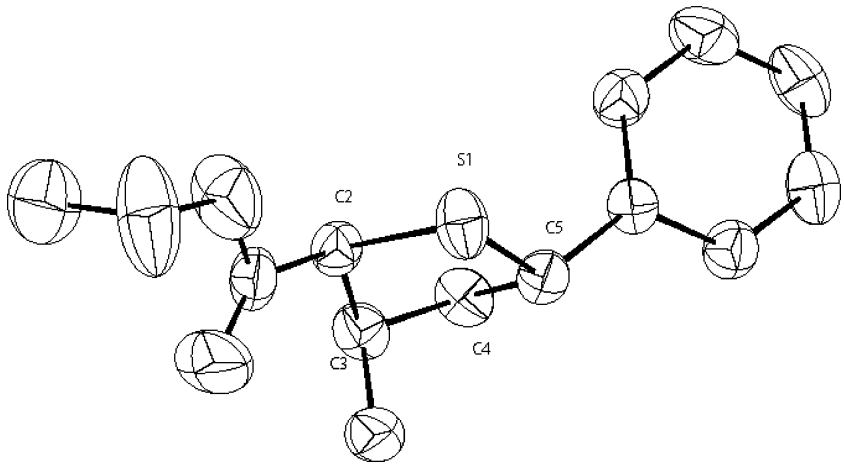


FIGURE 2 ORTEP drawing of ethyl (2*R*,3S,5R)/(2*S*,3*R*,5*S*)-3-hydroxy-5-phenyl-tetrahydrothiophene-2-carboxylate (**2d**).

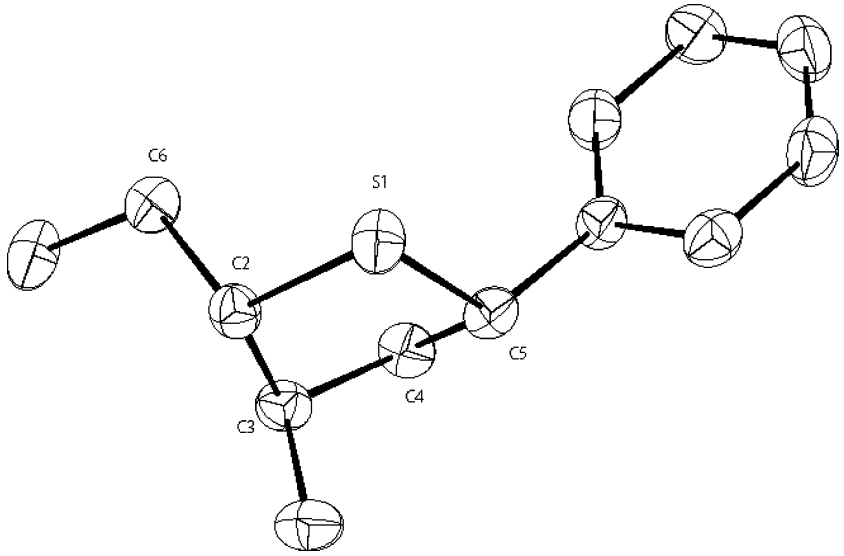


FIGURE 3 ORTEP drawing of (2*R*,3*S*,5*R*)/(2*S*,3*R*,5*S*)-2-hydroxymethylene-3-hydroxy-5-phenyl-tetrahydrothiophene (**3a**).

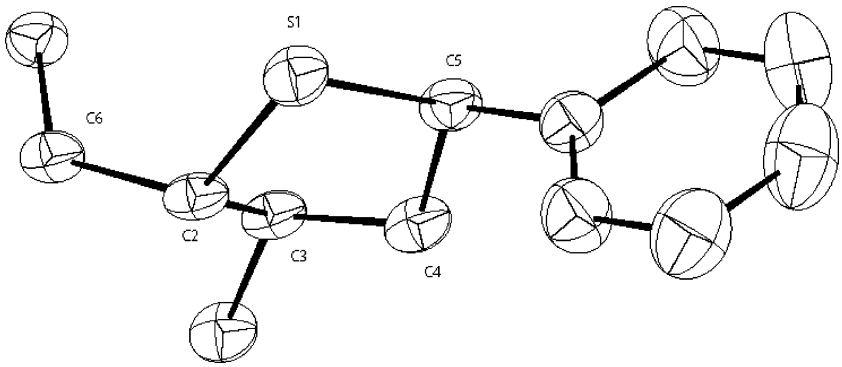


FIGURE 4 ORTEP drawing of (2*S*,3*R*,5*R*)/(2*R*,3*S*,5*S*)-2-hydroxymethylene-3-hydroxy-5-phenyl-tetrahydrothiophene (**3b**).

CONCLUSION

We have synthesized isomeric tetrahydrothiophene derivatives **2a**–**2d** by a single two-step/one-pot tandem reaction with good yields. While tertiary Lewis bases favor the formation of isomer **2d**, secondary amines favor the formation of **2c**. From these result it is concluded that during the ring closure, the approach *ul* [C2(*Si*)/C3(*Re*)] or [C2(*Re*)/C3(*Si*)] of the enolate to the aldehyde, which gives rise to products **2c** and **2d** respectively, is lower in energy than the alternative approach *lk* [C2(*Si*)/C3(*Si*)] or [C2(*Re*)/C3(*Re*)] which leads to products **2a** and **2b**, respectively. The configuration of these isomers and their reduction products (**3a–3d**) was assigned from vicinal $^3J_{HH}$ coupling constants and confirmed by the X-ray structure of isomeric **2d, 3a**, and **3b** isomers. Most of the compounds adopt twist conformations in solution and in solid state; however, the aromatic *C*-thionucleoside **3a**, which presents the configuration of natural nucleosides, tends to adopt an *envelope* conformation in the solid state. By the same token, the conformation suggested by vicinal $^3J_{HH}$ coupling constants of **2a** in solution corresponds to an *envelope*. The aromatic *C*-thionucleoside **3d** was submitted to the National Cancer Institute in Maryland for its in vitro testing assay in cell line CEM-SS, and it was found inactive (IC50(molar) $> 2.00 \times 10^{-4}$). Finally, it is worth noting that the strategy reported in Scheme 3 for the synthesis of aromatic *C*-thionucleosides merits to be explored for the synthesis of thionucleosides with new or proved antiviral properties, in view of its simplicity. We are now focusing our work in this endeavor.

EXPERIMENTAL

Melting points are uncorrected. Nuclear magnetic resonance spectra were recorded on Jeol Eclipse 270 spectrometer at 270 MHz for ^{1}H and at 67.5 MHz for ^{13}C. Mass spectra (EI) were measured on a Hewlett Packard 5989A spectrometer using electron impact (EI) at 70 eV. The reactions were performed under nitrogen atmosphere in oven-dried glassware. Solvent and solutions were transferred by syringe-septum and cannula techniques. Solvents for reactions were reagent grade; tetrahydrofuran, diethyl ether, and benzene were dried and distilled immediately before use from sodium/benzophenone. Methylene chloride was dried and distilled from drierite. Lewis bases were dried and distilled from $LiAlH_4$. Products were purified by flash column chromatography on silica gel 230–400 mesh. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Crystallographic work was performed in an Enraf-Nonius CAD-4 diffractometer. Data collection was done using CAD-4 software [20]. Cell refinement was done with CAD-4 software. For data reduction JANA96 [21] was used. The structures were solved and refined by CRYSTALS [22]. For molecular graphics CAMERON [23] and for dihedral angles PARST 95 [24] were used. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications numbers for structure 2d (CCDC 291603), for 3a (CCDC 291602) and for 3b (CCDC 291604).

Synthesis of Ethyl 3-hydroxy-5-phenyl-tetrahydrothiophene-2-carboxylates **2a–2d**

To a solution of 12.6 mL (0.1 mol) of *trans*-cinnamaldehyde and 11.0 mL (0.1 mol) of ethyl 2-mercaptoacetate in 50 mL of dry THF, was added 13.9 mL (0.1 mol) of triethylamine. The mixture was stirred under reflux for 24 h. When the time was complete, the mixture was cooled to room temperature and it was washed with water and brine. The combined organic extracts were dried with (anh.) sodium sulfate, filtered, and concentrated in a rotary evaporator. The oily product was chromatographed on silica gel using a mixture of (98:2) hexane/ethyl

acetate as eluent. The relative proportion of **2a–2d** was determined by ^{1}H and eventually by ^{13}C NMR.

2a: (2*S*,3*S*,5*R*)/(2R,3*R*,5S). R_f 0.44 [(7:3) hexane/ethyl acetate]. Oily product. ^{1}H NMR ($CDCl_3$) δ 1.31 (t, $^3J_{HH} = 7.3$ Hz, 3H, CH_3), 2.47 (ddd, $^3J_{4a\text{-}5} = 8.3$ Hz, $^3J_{4a\text{-}3} = 1.0$ Hz, $J_{gem} = 11.6$ Hz, 1H, H4a), 2.50 (ddd, $^3J_{4b\text{-}5} = 8.9$ Hz, $^3J_{4b\text{-}3} = 1.6$ Hz, $J_{gem} = 11.6$ Hz, 1H, H4b), 3.97 (d, $^3J_{2\text{-}3} = 2.0$ Hz, 1H, H2), 4.04 (bs, 1H, OH), 4.23 (c, $^3J_{HH} = 7.3$ Hz, 2H, CH_2), 4.82 (dd, $^3J_{5\text{-}4a} = 8.3$ Hz, $^3J_{5\text{-}4b} = 8.9$ Hz, 1H, H5), 4.85 (m, 1H, H3), 7.28 (m, 3H, arom.), 7.43 (m, 2H, arom.); ^{13}C NMR ($CDCl_3$) δ 14.07 (CH_3), 46.52 (C4), 50.76 (C5), 56.86 (C2), 61.55 (CH_2), 76.84 (C3), 127.49 (C_p), 127.94 (C_m), 128.64 (C_o), 140.49 (C_i), 172.23 (C=O); MS (*m*/*z*) 252 (M^+), 208 ($M^+ - 44$), 201 ($M^+ - 51$), 161 ($M^+ - 91$), 133 ($M^+ - 119$), 117 ($M^+ - 135$), 105 ($M^+ - 147$), 77 ($M^+ - 175$), 45 ($M^+ - 207$), 29 ($M^+ - 223$); Anal. Calcd for $C_{13}H_{16}SO_3$: C, 61.88; H, 6.39. Found: C, 61.72; H, 6.39.

2b: (2R,3*R*,5R)/(2*S*,3*S*,5*S*). R_f 0.35 [(7:3) hexane/ethyl acetate]. White flakes of mp 60–62°C. ^{1}H NMR ($CDCl_3$) δ 1.29 (t, $^3J_{HH} = 7.3$ Hz, 3H, CH_3), 2.28 (ddd, $^3J_{4a\text{-}5} = 10.2$ Hz, $^3J_{4a\text{-}3} = 9.6$ Hz, $J_{gem} = 12.5$ Hz, 1H, H4a), 2.71 (ddd, $^3J_{4b\text{-}5} = 5.9$ Hz, $^3J_{4b\text{-}3} = 5.3$ Hz, $J_{gem} = 12.5$ Hz, 1H, H4b), 3.97 (bs, 1 H, OH), 4.08 (d, $^3J_{2\text{-}3} = 7.3$ Hz, 1H, H2), 4.22 (c, $^3J_{HH} = 7.3$ Hz, 2H, CH_2), 4.63 (dd, $^3J_{5\text{-}4a} = 10.2$ Hz, $^3J_{5\text{-}4b} = 5.9$ Hz, 1H, H5), 4.75 (ddd, $^3J_{3\text{-}4a} = 9.6$ Hz, $^3J_{3\text{-}4b} = 5.3$ Hz, $^3J_{3\text{-}2} = 7.3$ Hz, 1H, H3), 7.29 (m, 3 H, arom.), 7.43 (m, 2H, arom.); ^{13}C NMR ($CDCl_3$) δ 14.03 (CH_3), 45.36 (C4), 47.44 (C5), 54.21 (C2), 61.76 (CH_2), 76.6 (C3), 127.53 (C_m), 127.60 (C_p), 128.59 (C_o), 140.52 (C_i), 171.95 (C=O); MS (*m*/*z*) 252 (M^+), 219 ($M^+ - 33$), 201 ($M^+ - 51$), 161 ($M^+ - 91$), 136 ($M^+ - 116$), 117 ($M^+ - 135$), 105 ($M^+ - 147$), 77 ($M^+ - 175$), 45 ($M^+ - 207$), 29 ($M^+ - 223$); Anal. Calcd for $C_{13}H_{16}SO_3$: C, 61.88; H, 6.39. Found: C, 61.84; H, 6.36.

2c: (2*S*,3*R*,5*R*)/(2*R*,3*S*,5*S*). R_f 0.41 [(7:3) hexane/ethyl acetate]. Oily product. ^{1}H NMR ($CDCl_3$) δ 1.27 (t, $^3J_{HH} = 7.3$ Hz, 3H, CH_3), 2.53 (ddd, $^3J_{4b\text{-}5} = 6.6$ Hz, $^3J_{4b\text{-}3} = 5.9$ Hz, $J_{gem} = 12.0$ Hz, 1H, H4b), 2.65 (dt, $^3J_{4a\text{-}5} = 10.6$ Hz, $^3J_{4a\text{-}3} = 10.6$ Hz, $J_{gem} = 12.0$ Hz, 1H, H4a), 3.77 (bs, 1H, OH), 3.99 (d, $^3J_{2\text{-}3} = 6.6$ Hz, 1H, H2), 4.22 (c, $^3J_{HH} = 7.3$ Hz, 2H, CH_2), 4.46 (dd, $^3J_{5\text{-}4a} = 10.6$ Hz, $^3J_{5\text{-}4b} = 6.6$ Hz, 1H, H5), 4.53 (ddd, $^3J_{3\text{-}4a} = 10.6$ Hz, $^3J_{3\text{-}4b} = 5.9$ Hz, $^3J_{3\text{-}2} = 6.6$ Hz, 1H, H3), 7.28 (m, 3H, arom.), 7.45 (m, 2H, arom.); ^{13}C NMR ($CDCl_3$) δ 14.04 (CH_3), 43.46 (C4), 46.80 (C5), 50.13 (C2), 61.47 (CH_2), 75.99 (C3), 127.47 (C_p), 127.81 (C_m), 128.48 (C_o), 141.24 (C_i), 172.96 (C=O); MS (*m*/*z*) 252 (M^+), 234 ($M^+ - 18$), 210 ($M^+ - 42$), 179 ($M^+ - 73$), 161 ($M^+ - 91$), 133 ($M^+ - 119$), 105 ($M^+ - 147$), 77 ($M^+ - 175$), 45 ($M^+ - 207$), 29 ($M^+ - 223$); Anal. Calcd for $C_{13}H_{16}SO_3$: C, 61.88; H, 6.39. Found: C, 61.72; H, 6.41.

2d: (2*R*,3S,5R)/(2*S*,3*R*,5*S*). R_f 0.45 [(7:3) hexane/ethyl acetate]. White crystals of mp 57–59°C. ^{1}H NMR ($CDCl_3$) δ 1.31 (t, $^3J_{HH} = 7.3$ Hz, 3H, CH_3), 2.06 (ddd, $^3J_{4a\text{-}5} = 10.6$ Hz, $^3J_{4a\text{-}3} = 3.3$ Hz, $J_{gem} = 13.2$ Hz, 1H, H4a), 2.60 (ddd, $^3J_{4b\text{-}5} = 5.9$ Hz, $^3J_{4b\text{-}3} = 2.6$ Hz, $J_{gem} = 13.2$ Hz, 1H, H4b), 3.82 (bs, 1H, OH), 4.25 (c, $^3J_{HH} = 7.3$ Hz, 2H, CH_2), 4.39 (d, $^3J_{2\text{-}3} = 4.0$ Hz, 1H, H2), 4.84 (ddd, $^3J_{3\text{-}4a} = 3.3$ Hz, $^3J_{3\text{-}4b} = 2.6$ Hz, $^3J_{3\text{-}2} = 4.0$ Hz, 1H, H3), 5.01 (dd, $^3J_{5\text{-}4a} = 10.6$ Hz, $^3J_{5\text{-}4b} = 5.9$ Hz, 1H, H5), 7.28 (m, 3H, arom.) 7.44 (m, 2H, arom.); ^{13}C NMR ($CDCl_3$) δ 13.54 (CH_3), 45.98 (C4), 50.24 (C5), 53.66 (C2), 61.24 (CH_2), 74.54 (C3), 126.90 (C_p), 127.19 (C_m), 128.04 (C_o), 140.50 (C_i), 171.06 (C=O); MS (*m*/*z*) 252 (M^+), 219 ($M^+ - 33$), 210 ($M^+ - 42$), 161 ($M^+ - 91$), 136 ($M^+ - 116$), 121 ($M^+ - 131$), 105 ($M^+ - 147$), 77 ($M^+ - 175$), 45 ($M^+ - 207$), 29 ($M^+ - 223$); Anal. Calcd for $C_{13}H_{16}SO_3$: C, 61.88; H, 6.39. Found: C, 61.83; H, 6.40.

Synthesis of 2-Hydroxymethylene-3-hydroxy-5-phenyl-tetrahydrothiophene **3a–3d**

To a solution of 0.13 g (3.0 mmol) of lithium aluminum hydride in 30 mL of dry Et_2O maintained at 0°C under stirring was transferred via a filter-tipped cannula a solution of the ester **2a** (or any other isomeric ester **2b–2d**) 0.77 g (3.0 mmol) in 30 mL of dry Et_2O. When the addition was complete, the mixture was warmed up to room temperature and it was stirred for additional 12 h. The resulting suspension was cooled to 0°C, and water was added drop wise (25 mL) followed by the addition of 30 mL of acetone. A precipitate was formed, and it was filtered off. The filtrate was concentrated in the rotary evaporator and the water was removed with a vacuum pump at 1 mmHg. The residue was further dried with anh. sodium sulfate; the solid was filter off and washed with acetone. The solvent was removed to yield yellow oil. The product was chromatographed on silica gel using a mixture of (80:20) hexane/ethyl acetate as eluent.

3a: (2*R*,3*S*,5*R*)/(2*S*,3*R*,5*S*). R_f 0.21 ((1:1) hexane/ethyl acetate). White crystals of mp 125–127°C (isolated yield 48.0%). ^{1}H NMR (acetone-d_6) δ 2.08 (ddd, $^3J_{4a\text{-}5} = 11.2$ Hz, $^3J_{4a\text{-}3} = 3.3$ Hz, $J_{gem} = 11.2$ Hz, 1H, H4a), 2.30 (ddd, $^3J_{4b\text{-}5} = 5.3$ Hz, $^3J_{4b\text{-}3} = 2.0$ Hz, $J_{gem} = 11.2$ Hz, 1H, H4b), 3.45 (ddd, $^3J_{2\text{-}3} = 1.3$ Hz, $^3J_{2\text{-}6a} = 6.6$ Hz, $^3J_{2\text{-}6b} = 6.6$ Hz, 1H, H_2), 3.62 (d, $^3J_{6a\text{-}2} = 6.6$ Hz, 1H, H6a), 3.64 (d, $^3J_{6b\text{-}2} = 6.6$ Hz, 1H, H6b), 4.14 (ddd, $^4J_{OH\text{-}H} = 2.0$ Hz, $^3J_{OH\text{-}H} = 5.9$ Hz, $^3J_{OH\text{-}H} = 5.9$ Hz, 1H, OH-6), 4.20 (dd, $^4J_{OH\text{-}H} = 2.0$ Hz, $^3J_{OH\text{-}H} = 3.6$ Hz, 1H, OH-3), 4.64 (ddd, $^3J_{3\text{-}4a} = 3.3$ Hz,

$^3J_{3\text{-}4b} = 2.0$ Hz, $^3J_{3\text{-}2} = 1.3$ Hz, 1H, H3), 4.77 (dd, $^3J_{5\text{-}4a} = 11.2$ Hz,$^3J_{5\text{-}4b} = 5.3$ Hz, 1H, H5), 7.27 (m, 3H, arom.), 7.37 (m, 2H, arom.); ^{13}C NMR (acetone-d_6) δ 46.20 (C4), 50.69 (C2), 60.55 (C5), 66.36 (C6), 76.82 (C3), 127.84 (C_p), 128.65 (C_m), 129.13 (C_o), 143.0 (C_i); MS (*m/z*) 210 (M^+), 192 ($M^+ - 18$), 161 ($M^+ - 49$), 135 ($M^+ - 75$), 121 ($M^+ - 89$), 105 ($M^+ - 105$), 77 ($M^+ - 133$), 51 ($M^+ - 159$), 31 ($M^+ - 179$), 29 ($M^+ - 181$); Anal. Calcd for $C_{11}H_{14}SO_2$: C, 62.83; H, 6.71. Found: C, 62.80; H, 6.68.

3b: (2*S*,3*R*,5*R*)/(2*R*,3*S*,5*S*). R_f 0.15 ((1:1) hexane/ethyl acetate). White crystals of mp 84–86°C (isolated yield 32.9%). ^{1}H NMR (acetone-d_6) δ 2.16 (ddd, $^3J_{4a\text{-}5} = 11.2$ Hz, $^3J_{4a\text{-}3} = 9.9$ Hz, $J_{gem} = 11.9$ Hz, 1H, H4a), 2.58 (ddd, $^3J_{4b\text{-}5} = 5.9$ Hz, $^3J_{4b\text{-}3} = 5.3$ Hz, $J_{gem} = 11.9$ Hz, 1H, H4b), 3.50 (bs, 2H, OH-3, OH-6), 3.58 (ddd, $^3J_{2\text{-}3} = 7.9$ Hz, $^3J_{2\text{-}6a} = 5.3$ Hz, $^3J_{2\text{-}6b} = 6.6$ Hz, 1H, H2), 3.68 (dd, $^3J_{6b\text{-}2} = 6.6$ Hz, $^3J_{gem} = 10.6$ Hz, 1H, H6b), 3.89 (dd, $^3J_{6a\text{-}2} = 5.3$ Hz, $^3J_{gem} = 10.6$ Hz, 1H, H6a), 4.24 (ddd, $^3J_{3\text{-}4a} = 9.9$ Hz, $^3J_{3\text{-}4b} = 5.3$ Hz, $^3J_{3\text{-}2} = 7.9$ Hz, 1H, H3), 4.51 (dd, $^3J_{5\text{-}4a} = 11.2$ Hz,$^3J_{5\text{-}4b} = 5.9$ Hz, 1H, H5), 7.28 (m, 3H, arom.), 7.44 (m, 2H, arom.); ^{13}C NMR (acetone-d_6) δ 46.93 (C4), 47.68 (C5), 57.57 (C2), 65.34 (C6), 77.47 (C3), 127.88 (C_p), 128.49 (C_m), 129.17 (C_o), 144.0 (C_i); MS (*m/z*) 210 (M^+), 179 ($M^+ - 31$), 161 ($M^+ - 49$), 136 ($M^+ - 74$), 121 ($M^+ - 89$), 105 ($M^+ - 105$), 77 ($M^+ - 133$), 51 ($M^+ - 159$), 31 ($M^+ - 179$), 29 ($M^+ - 181$); Anal. Calcd for $C_{11}H_{14}SO_2$: C, 62.83; H, 6.71. Found: C, 62.81; H, 6.69.

3c: (2*R*,3*R*,5*R*)/(2*S*,3*S*,5*S*). R_f 0.29 ((1:1) hexane/ethyl acetate). Oily product (isolated yield 46.7%). ^{1}H NMR ($CDCl_3$) δ 2.26 (ddd, $^3J_{4a\text{-}5} = 10.6$ Hz, $^3J_{4a\text{-}3} = 10.9$ Hz, $J_{gem} = 12.5$ Hz, 1H, H4a), 2.52 (ddd, $^3J_{4b\text{-}5} = 5.9$ Hz, $^3J_{4b\text{-}3} = 5.6$ Hz, $J_{gem} = 12.5$ Hz, 1H, H4b), 3.35 (bs, 2H, OH-3, OH-6), 3.58 (ddd, $^3J_{2\text{-}3} = 5.3$ Hz, $^3J_{2\text{-}6a} = 8.6$ Hz, $^3J_{2\text{-}6b} = 4.0$ Hz, 1H, H2), 3.78 (dd, $^3J_{6b\text{-}2} = 4.0$ Hz, $^3J_{gem} = 11.9$ Hz, 1H, H6b), 4.06 (dd, $^3J_{6a\text{-}2} = 8.6$ Hz, $^3J_{gem} = 11.9$ Hz, 1H, H6a), 4.40 (dd, $^3J_{5\text{-}4a} = 10.6$ Hz,$^3J_{5\text{-}4b} = 5.9$ Hz, 1H, H5), 4.64 (ddd, $^3J_{3\text{-}4a} = 10.9$ Hz, $^3J_{3\text{-}4b} = 5.6$ Hz, $^3J_{3\text{-}2} = 5.3$ Hz, 1H, H3), 7.30 (m, 3H, arom.), 7.39 (m, 2H, arom.); ^{13}C NMR ($CDCl_3$) δ 43.58 (C4), 46.09 (C5), 50.06 (C2), 63.93 (C6), 76.60 (C3), 127.58 (C_p), 127.83 (C_m), 128.59 (C_o), 141.57 (C_i); MS (*m/z*) 210 (M^+), 192 ($M^+ - 18$), 162 ($M^+ - 48$), 121 ($M^+ - 89$), 105 ($M^+ - 105$), 77 ($M^+ - 133$), 45 ($M^+ - 165$), 31 ($M^+ - 179$); Anal. Calcd for $C_{11}H_{14}SO_2$: C, 62.83; H, 6.71. Found: C, 62.75; H, 6.68.

3d: (2*S*,3*S*,5*R*)/(2*R*,3*R*,5*S*). R_f 0.18 ((1:1) hexane/ethyl acetate). White crystals of mp 134–135°C (isolated yield 45%). ^{1}H NMR (acetone-d_6) δ 2.10 (ddd, $^3J_{4a\text{-}5} = 10.6$ Hz, $^3J_{4a\text{-}3} = 3.3$ Hz, $J_{gem} = 12.9$ Hz, 1H, H4a), 2.41 (ddd, $^3J_{4b\text{-}5} = 5.3$ Hz, $^3J_{4b\text{-}3} = 2.3$ Hz, $J_{gem} = 12.9$ Hz, 1H, H4b), 3.72 (m, 1H, H2), 3.95 (d, $^3J_{6a\text{-}2} = {}^3J_{6b\text{-}2} = 6.6$ Hz, 2H, H_{6a} and H6b), 3.97 (bs, 1H, OH-6), 4.21 (d, $^3J_{OH\text{-}H} = 4.6$ Hz, 1H, OH-3), 4.72 (m, 1H, H3), 4.81 (dd, $^3J_{5\text{-}4a} = 10.6$ Hz,$^3J_{5\text{-}4b} = 5.3$ Hz, 1H, H5), 7.36 (m, 3H, arom.), 7.50 (m, 2H, arom.); ^{13}C NMR (acetone-d_6) δ 48.75 (C4), 50.13 (C_5), 56.90 (C2), 62.40 (C6), 76.72 (C3), 128.2 (C_m), 127.44 (C_p), 128.79 (C_o), 142.95 (C_i); MS (*m/z*) 210 (M^+), 192 ($M^+ - 18$), 161 ($M^+ - 49$), 136 ($M^+ - 74$), 129 ($M^+ - 81$), 104 ($M^+ - 106$), 73 ($M^+ - 137$), 44 ($M^+ - 166$), 29 ($M^+ - 181$); Anal. Calcd for $C_{11}H_{14}SO_2$: C, 62.83; H, 6.71. Found: C, 62.76; H, 6.71.

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