SYNTHESES OF 4-ACETOXY- OR ACETYLTHIO-2-SUBSTITUTED TETRAHYDROTHIOPHENE

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Abstract – The generality of a three-step route for the preparation of 4-acetoxy-2-alkyltetrahydrothiophenes was investigated, which started from 1-alken-4-ols including epoxidation, mesylation and intramolecular nucleophilic substitution. 4-Acetoxy-2-alkyltetrahydrothiophenes could be produced in moderate to good yields by this method, even a bulky substituted group on the C-4 position of 1-alken-4-ol did not make significant effect on the reaction. In contrast, 1-alken-4-ols with an aryl group attached to the C-4 position gave acyclic products 1,4-diacetylthio-4-arylbutan-2-yl acetates when the reactions were carried out in acetonitrile under reflux. Whereas, 4-acetylthio-2-aryltetrahydrothiophenes were obtained in good yields when the reactions were carried out in toluene under reflux. A possible pathway for the latter involving an intermediate of episulfide was proposed.

INTRODUCTION

Substituted tetrahydrothiophenes have been reported to serve as important structural motifs in many biologically active molecules. The essential coenzyme biotin as a water-soluble vitamin with important biological functions[1] is very representative, which is produced on large scale by chemical synthesis. Many non-natural tetrahydrothiophenes have been designed and prepared for their potential pharmacological properties, such as 3′-hetero-dideoxynucleoside analogues,[2] modified dideoxy-isonucleosides,[3] iso-4-thionucleosides.[4] Their derivatives, such cyclic sulfonium salts[5] and the related cyclic sulfolanes,[6] also display important biologically activities. In addition, tetrahydrothiophenes are also important intermediates for the production of thiophenes through dehydration and aromatization.[7] In view

of the importance of tetrahydrothiophene scaffold, the topic about its syntheses has been emerged as an important research area in the past decade.[8] A wide variety of approaches have been developed to produce chiral non racemic tetrahydrothiophenes[8b] or the racemates.[9] However, there are still many challenges for the availability of both racemic and non racemic tetrahydrothiophenes despite the various versions of the approaches to these compounds.

In our previous work about the synthesis of flavor compounds with 1,3-oxygen-sulfur functionality, a three-step synthetic route for 4-acetoxy-2-propyltetrahydrothiophene was achieved starting from 1-hepten-4-ol through epoxidation and mesylation to 1, 2-epoxy-4-heptyl mesylate and then reaction with thioacetate in an ideal yield (Scheme 1).[10] Compared with the preparation methods for the similar tetrahydrothiophens,[2,6,11] the synthetic route we discovered fortuitously was more straightforward. In order to expand the scope of this reaction, more substrates with various substituted groups have been investigated in this work by starting from a series of homoallylic alcohols **1** (Scheme 1).
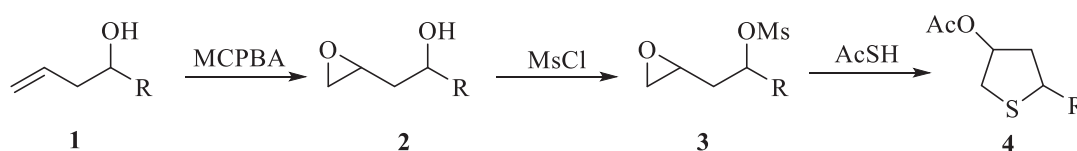
Scheme 1

RESULTS AND DISCUSSION

As shown in Scheme 1, a series of 1,2-epoxy-4-alkyl mesylates (**3a-f**) were prepared by starting from the corresponding homoallylic alcohols (**1a-f**) through epoxidation and mesylation. All the alcohols except commercially available 1-penten-4-ol (**1a**) were obtained in >83% yields by the Grignard reaction of allylmagnesium chloride with the corresponding aldehydes. The epoxidation of **1a-f** was carried out with *m*-CPBA to give the intermediates 1,2-epoxy-4-alkanols (**2a-f**) in >89% yields with very close diastereomeric ratio of about 1:1, which were converted to the corresponding 1,2-epoxy-4-alkyl mesylates (**3a-f**) in >72% yields. The 1,2-epoxy-4-alkyl mesylates obtained were then treated with 1.4 eq. of AcSH in the presence of K_2CO_3 in MeCN under reflux, and the results were shown in Table 1.

Unexpectedly, the reactions of 6 substrates (**3a-f**) under investigation were divided into two groups based on the results, one of which gave tetrahydrothiophenes (**4**) (Entries 1-4) and the other gave acyclic products (**5**) (Entries 5 and 6). For the substrates **3a** and **3b** (Entries 1 and 2), the tetrahydrothiophenes were obtained in >80% yields, which were very close to that of 2-propyl-4-acetoxytetrahydrothiophene in our previous work.[10] In contrast, the substrates **3c** and **3d** (Entries 3 and 4) gave the tetrahydrothiophenes in relatively lower yields of 60-70%, which might be due to the effects of the bulky groups on the reactions. All the tetrahydrothiophenes were produced as mixtures of *cis*- and *trans*-isomers with

approximately equal amounts, which were separated on silica column except 2-methyl-4-acetoxytetrahydrothiophene (**4a**). Only a little amount of pure separated isomers of **4a** were obtained for NMR analyses. The relative configurations of the tetrahydrothiophenes **4a-d** obtained were determined via the NOE experiments just as what was done in our previous work.[10] In addition, a by-product, 5-acetoxy-6-acetylthio-2-methyl-2-hexene (**6**) was obtained in 12% yield for the substrate **3c**, which was supposed to be formed via an elimination followed by the epoxy ring opening (Scheme 2). As shown in Scheme 2, the attack of AcS⁻ on the epoxy ring gave 1-acetylthio-5-methyl-4-hexen-2-yloxy anion, which underwent an intramolecular acetyl migration and an intermolecular acetyl migration sequentially to afford **6**. These kinds of intra- and intermolecular acetyl migration were also reported in the reference about trimethylamine catalyzed S → O acetyl migration reaction.[12]

**Table 1.** The reaction of 1,2-epoxy-4-alkyl mesylates with AcSH

Entry	Substrate[a]	Product (yield, %)		
		4	**5**	**10**
1	**3a**, R = Me	*cis*- and *trans*-**4a**, 81%		
2	**3b**, R = *n*-hexyl	*cis*-**4b**, 39%; *trans*-**4b**, 43%		
3	**3c**, R = *i*-propyl	*cis*-**4c**, 35%; *trans*-**4c**, 31%		
4	**3d**, R = *t*-butyl	*cis*-**4d**, 34%; *trans*-**4d**, 31%		
5	**3e**, R = phenyl	**5a**, 42%[b]		
6	**3f**, R = *p*-methylphenyl	**5b**, 38%[b]		
7	**3e**, R = phenyl	**10a**, 82%[b]		
8	**3f**, R = *p*-methylphenyl	**10b**, 80%[b]		

[a] The experiments of Entries 7 and 8 were carried out in toluene, while the others in MeCN. [b] 2.4 eq. of AcSH was used.
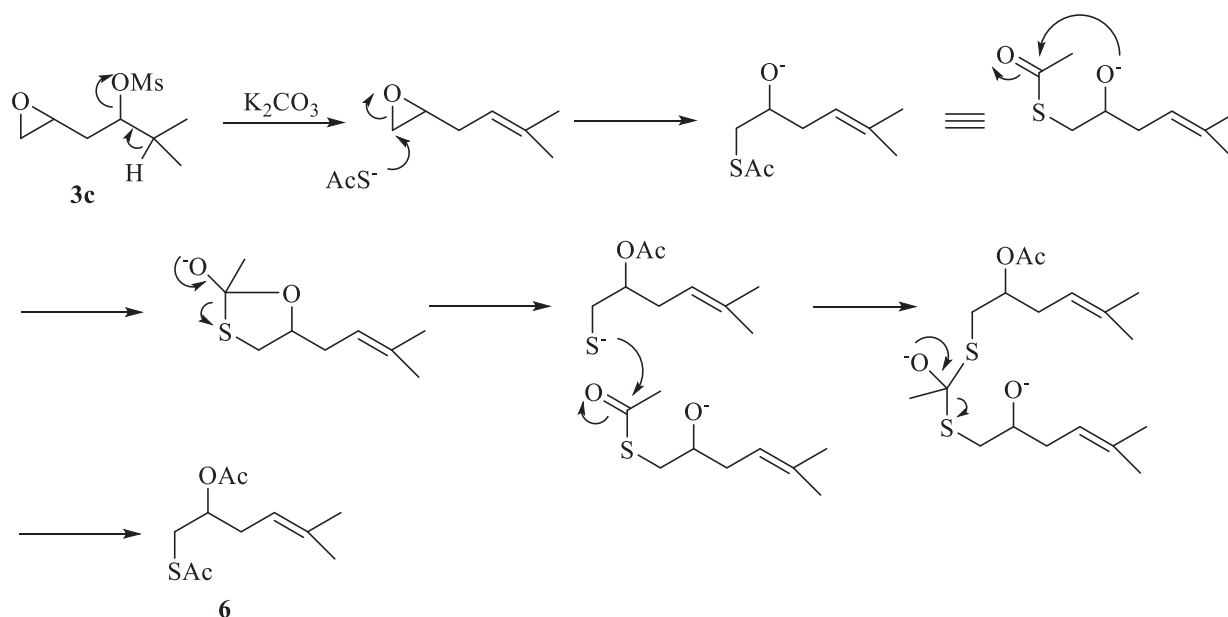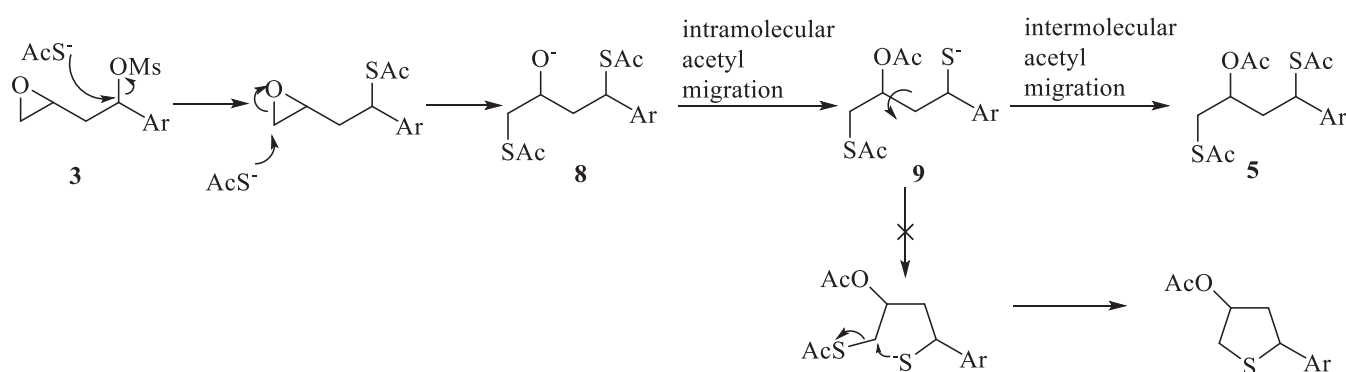
Scheme 2

Two substrates containing aryl groups **3e** and **3f** failed to afford the corresponding tetrahydrothiophenes as expected and produced 1,4-diacetylthio-4-arylbutan-2-yl acetates **5a** and **5b** instead by treatment with 2.4 eq. of AcSH (Entries 5 and 6). Initially, the substrate 1,2-epoxy-4-phenylbutan-4-yl mesylate (**3e**) was treated with 1.4 eq. of AcSH under the conditions the same as those for the substrates **3a-d**, which gave 1,4-diacetylthio-4-phenylbutan-2-yl acetate (**5a**) in 21% yield and 1,2-epoxy-4-acetylthio-4-phenylbutane (**7**) in 34% yield (Scheme 3). The latter **7** was converted to **5a** when it was treated further with 1.2 eq. of AcSH in the presence of K_2CO_3. Therefore, 2.4 eq. of AcSH were adopted in our further experiments and a single product **5** was obtained in about 40% yield for both substrates **3e** and **3f**.
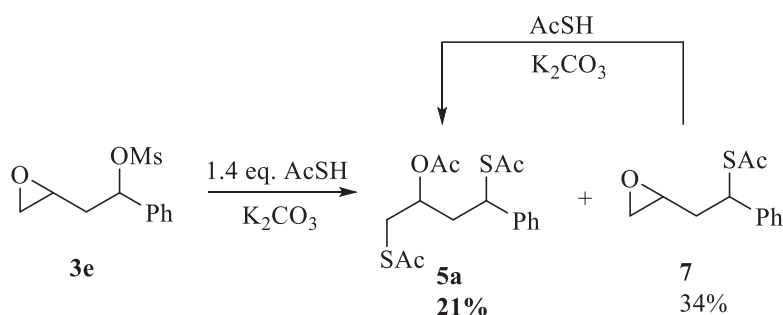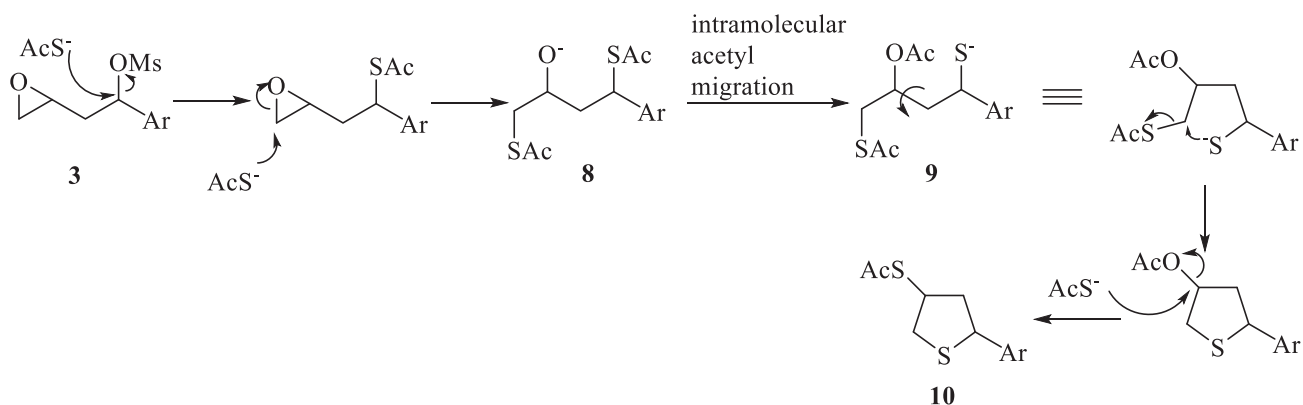

Scheme 3

The possible pathway of formation of 1,4-diacetylthio-4-arylbutan-2-yl acetates (**5a** and **5b**) was shown in Scheme 4. 1,2-Epoxy-4-arylbutan-4-yl mesylate (**3**) was attacked by two equivalents of AcS⁻ sequentially, which led to the substitution of the mesyl group and the opening of the epoxy ring to give

the intermediate 1,4-diacetylthio-4-aryl-2-butoxyl anion (**8**). An intramolecular acetyl migration occurred to this intermediate to produce the corresponding alkylsulphanyl anion (**9**), which then underwent an intermolecular acetyl migration to afford **5**. The reason that the intermediate alkylsulphanyl anion (**9**) failed to give the tetrahydrothiophene as expected was assumed as follows. In our previous study, the alkylsulphanyl anion (**9**) reached an optimal conformation suitable for the intramolecular nucleophilic substitution via C-C single bond free rotation, which then produced a tetrahyrothiophene ring.[10] In the present case, the presence of an aryl group was suspected to obstruct this kind of C-C single bond free rotation incapable of reaching an optimal formation for the intramolecular nucleophilic substitution.
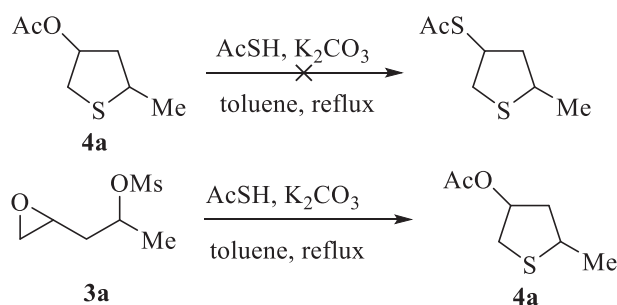

Scheme 4

Based on the above postulation, high reaction temperature was supposed to favor the formation of the tetrahydrothiophene ring. A reaction of the substrate **3e** was tried in toluene under reflux with 1.4 eq. of AcSH. Strangely, two unknown products were obtained in about 45% yield instead of 2-phenyl-4-acetoxytetrahydrothiophene. These two products were not able to separate on column and looked like a pair of stereoisomers with a ratio of about 1:1 based on the NMR data, which were further determined to be *cis*- and *trans*-isomers of 2-phenyl-4-acetylthiotetrahydrothiophene (**10a**) combined with the HRMS data. Obviously, the formation of these products required two equivalents of AcSH at least, so the experiment with 2.4 eq. of AcSH was then carried out. As expected, 2-phenyl-4-acetylthiotetrahydrothiophene (**10a**) was obtained in a higher yield of 82% (Entry 7). Likewise, the substrate **3f** gave 2-*p*-methylphenyl-4-acetylthiotetrahydrothiophene (**10b**) in 80% yield (Entry 8). Initially, we thought that 2-aryl-4-acetoxytetrahydrothiophene was produced first, which was then attacked by AcS⁻ via a nucleophilic substitution of the acetoxy group to give **10** (Scheme 5).
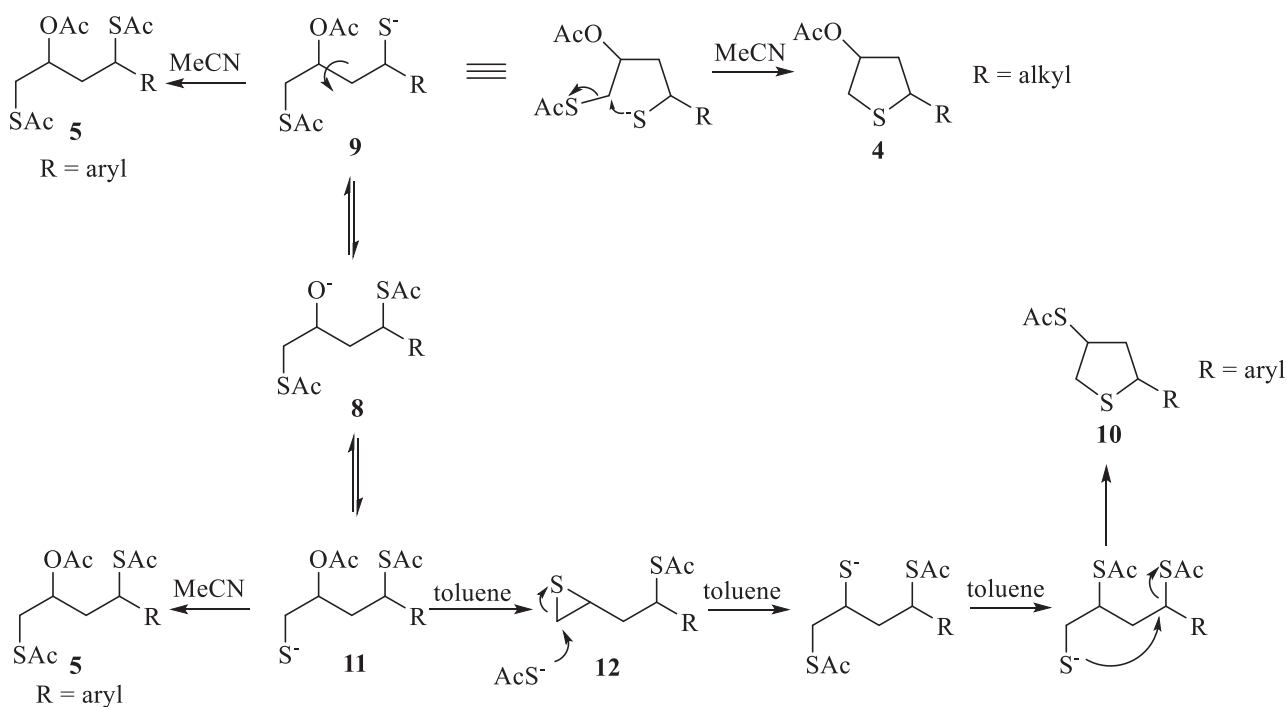
Scheme 5

2-Methyl-4-acetoxytetrahydrothiophene was treated with AcSH in the presence of K_2CO_3 in toluene under reflux in order to prove the above possibility. However, 2-methyl-4-acetylthiotetrahydrothiophene was not observed as we expected. Moreover, the reaction of the substrate **3a** with AcSH in toluene under reflux still gave 2-methyl-4-acetoxytetrahydrothiophene, not 2-methyl-4-acetylthiotetrahydrothiophene (Scheme 6). Compared with the experiment in acetonitrile of Entry 1, it completed within a shorter reaction time of about 5 h with a similar yield of 84%. These results excluded the possibility outlined in Scheme 5. There was no 2-aryl-4-acetoxytetrahydrothiophene produced as an intermediate, which could not undergo a nucleophilic substitution of the acetoxy group by AcS^-.

Scheme 6

It was a little strange that the reactions of the substrates (**3**) containing different substituted groups gave different products. How were 2-aryl-4-acetylthiotetrahydrothiophenes produced? A possible pathway was proposed as follows (Scheme 7). After two sequential nucleophilic attacks of AcS^- on the substrate (**3**), the intermediate (**8**) obtained underwent an intramolecular acetyl migration via two different ways. The acetyl group of acetylthio group located on the C-4 position would migrate via a six-member ring to give an intermediate (**9**), or the acetyl group located on the C-1 positon would migrate via a five-member ring to give an intermediate (**11**). The two migrating processes of acetyl group went fast and reached an

equilibrium state. When R was an alkyl group, the intermediate (**9**) underwent an intramolecular nucleophilic substitution, which led to the formation of 2-alkyl-4-acetoxytetrahydrothiophene (**4**). In contrast, this intramolecular nucleophilic substitution failed to occur when R was an aryl group, which might be due to the weak nucleophilicity of sulfide ion caused by the n-π action between the sulfide ion and aryl ring. Therefore, the intermediate **9** or **11** captured an acetyl group via an intermolecular acetyl migration to give the acyclic product (**5**) if the reaction was carried in MeCN under reflux. However, if the reaction underwent at higher temperature in toluene, the sulfide ion on the C-1 positon of the intermediate (**11**) could attack the C-2 position with an acetoxy group via an intramolecular nucleophilic substitution to produce a key intermediate of episulfide (**12**), which reacted with one more eq. of AcSH to give the product (**10**).

Scheme 7

One synthetic route of 2-phenyl-4-acetylthiotetrahydrothiophene was designed by starting from 1,2-epoxy-4-phenyl-4-butanol via episulfides as the intermediates (Scheme 8). 1,2-Epoxy-4-phenyl-4-butanol (**2e**) was converted into 1,2-epithio-4-phenyl-4-butanol (**13**) in about 84% by treatment with thiourea in the presence of Ti(Oi-Pr)$_4$, the hydroxyl group of which was then mesylated with MsCl. The synthesized 1,2-epithio-4-phenyl-4-butyl mesylate was treated with 2.4 eq. of AcSH in the presence of K$_2$CO$_3$ in toluene under reflux to afford the product (**10a**) in 77% yield with a

diastereomeric ratio of about 1:1 as we expected. The result indicated that the formation pathway of 2-aryl-4-acetylthiotetrahydrothiophene outlined in Scheme 7 was possible.
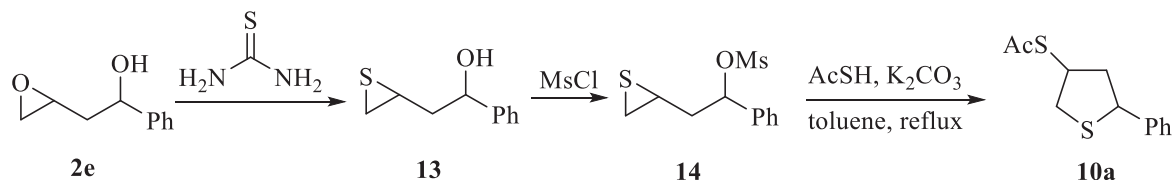
Scheme 8

In summary, tetrahydrothiophene rings could be constructed by starting from 1-alken-4-ols through epoxidation, mesylation and nucleophilic substitution with AcSH. 1-Alken-4-ols with alkyl groups on the C-4 postion produced 2-alkyl-4-acetoxytetrahydrothiophenes in acetonitrile in moderate to good yields, whereas those with aryl groups gave 2-aryl-4-acetylthiotetrahydrothiophenes in toluene in good yields. An intermediate of episulfide should exist in the formation of 2-aryl-4-acetylthiotetrahydrothiophene. The other 1-alken-4-ols with aryl groups on the C-4 position containing electron donating or electron withdrawing substituent groups are still under investigation in order to confirm further the application scope of this method. This approach for the synthesis of 2,4-disubstituted tetrahydrothiophene rings looks very attractive owing to several advantages, including the availability of 1-alken-4-ols, easy operation and ideal yields for each step, which should offer one more alternative for the preparation of these compounds.

EXPERIMENTAL

Allyl chloride (98%) and *m*-chloroperoxybenzoic acid (*m*-CPBA, 70%) were purchased from Beijing Bailingwei Science and Technology Company (Beijing, China). The others were purchased from Beijing Huaxue Shiji Company (Beijing, China). Compound **1a** is commercially available and purchased from Sigma-Aldrich. NMR spectra were obtained on a Bruker AV300 or 600 MHz NMR (^{1}H NMR at 300 or 600 MHz, ^{13}C NMR at 75 or 150 MHz) in CDCl$_3$ using TMS as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. The high resolution mass spectrum was performed on a SolariX Mass Spectrometer.

Typical Procedure for the Synthesis of Homoallylic Alcohols 1. All the homoallylic alcohols used in this work, except commercially available 1-penten-4-ol (**1a**), were prepared via the Grignard reaction of allylmagnesium chloride with the corresponding aldehyde according to the following procedure. Magnesium turnings (3.8 g, 0.16 mol) were covered by dry Et$_2$O (40 mL) and stirred vigorously under an

atmosphere of nitrogen. A small crystal of iodine was added, followed by allyl chloride (1.0 mL, 12 mmol). The mixture was heated to induce reaction, and further allyl chloride (7.7 g, 0.1 mol) in Et_2O (40 mL) was added at such a rate that the solution continued to reflux. After addition, Et_2O (40 mL) was added and the mixture was kept refluxing for 0.5 h. After cooling to room temperature, the solution of the aldehyde (0.1 mol) in dry Et_2O (30 mL) was added dropwise to the obtained solution of allylmagnesium chloride at room temperature. The reaction mixture was stirred for another 1 h under reflux after addition. The mixture was then cooled to room temperature and quenched with saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated. The residue distilled under vacuum to yield a colorless or light yellow liquid homoallylic alcohol (**1b-f**).

1-Decen-4-ol (1b): colorless oil; yield: 13.6 g (87%) yield; bp 79-81 °C /0.133 kPa. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.88 (t, J = 6.9 Hz, 3 H, Me), 1.18-1.52 (m, 10 H, HC5~HC9), 1.60 (d, J = 7.5 Hz, 1 H, -OH), 2.12 (m, 1 H, HC3), 2.30 (m, 1 H, HC3), 3.64 (m, 1 H, HC4), 5.13 (m, 2 H, HC1), 5.80 (m, 1 H, HC2). ^{13}C NMR (75 MHz, CDCl$_3$): δ 14.03 (Me), 22.59 (C9), 25.61 (C6), 29.32 (C7), 31.81 (C8), 36.77 (C5), 41.91 (C3), 70.66 (C4), 117.79 (C1), 134.97 (C2). All measured values were identical to those in the literature.[13]

5-Methyl-1-hexen-4-ol (1c): colorless oil; yield: 10.0 g (88%); bp 24-26 °C /0.036 kPa. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.89 and 0.90 (d, J = 6 Hz, 6 H, HC6), 1.65 (m, 1 H, HC5), 1.83 (s, 1 H, -OH), 2.08 (m, 1 H, HC3), 2.27 (m, 1 H, HC3), 3.36 (m, 1 H, HC4), 5.06 (d, J = 10.8 Hz, 1 H, HC1), 5.11 (d, J = 16.2 Hz, 1 H, HC1), 5.81 (m, 1 H, HC2). ^{13}C NMR (75 MHz, CDCl$_3$): δ 17.46 and 18.66 (C6), 33.03 (C5), 38.79 (C3), 75.36 (C4), 117.67 (C1), 135.47 (C2). All measured values were identical to those in the literature.[14]

5,5-Dimethyl-1-hexen-4-ol (1d): colorless oil; yield: 10.1 g (83%); bp 25-27 °C /0.050 kPa. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.92 (s, 9 H, HC6), 1.67 (s, 1 H, -OH), 1.98 (m, 1 H, HC3), 2.37 (m, 1 H, HC3), 3.25 (dd, J = 10.5, 1.5 Hz, 1 H, HC4), 5.12 (d, J = 11.1 Hz, 1 H, HC1), 5.13 (d, J = 16.5 Hz, 1H, HC1), 5.86 (m, 1 H, HC2). ^{13}C NMR (75 MHz, CDCl$_3$): δ 25.71 (C6), 34.59 (C5), 36.53 (C3), 78.10 (C4), 117.68 (C1), 136.56 (C2). All measured values were identical to those in the literature.[15]

4-Phenyl-1-buten-4-ol (1e): light yellow oil; yield: 2.7 g (86%); bp 52-54 °C /0.94 kPa. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.11 (s, 1 H, -OH), 2.52 (m, 2 H, HC3), 4.73 (dd, J = 7.2, 5.4 Hz, 1 H, HC4), 5.16 (m, 2 H, HC1), 5.81 (m, 1 H, HC2), 7.24-7.41 (m, 5 H, phenyl). ^{13}C NMR (75 MHz, CDCl$_3$): δ 43.78 (C3), 73.43 (C4), 118.17 (C1), 125.97 (C2′ and C6′ (phenyl)), 127.54 (C4′ (phenyl)), 128.42 (C3′ and C5′ (phenyl)), 134.62 (C2), 144.04 (C1′ (phenyl)). All measured values were identical to those in the literature.[15]

4-*p*-Methylphenyl-1-buten-4-ol (1f): light yellow oil; yield: 13.4 g (83%); bp 84-86 ºC /0.18 kPa. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.02 (br, 1 H, -OH), 2.36 (s, 3 H, Me), 2.52 (m, 2 H, HC3), 4.72 (t, *J* = 6.3 Hz, 1 H, HC4), 5.17 (m, 2 H, HC1), 5.83 (m, 1 H, HC2), 7.18 (d, *J* = 7.8 Hz, 2 H, HC3′ and HC5′ (phenyl)), 7.27 (d, *J* = 7.8 Hz, 2 H, HC2′ and HC6′ (phenyl)). ^{13}C NMR (75 MHz, CDCl$_3$): δ 21.18 (Me), 43.75 (C3), 73.30 (C4), 118.06 (C1), 125.90 (C2′ and C6′ (phenyl)), 129.10 (C3′ and C5′ (phenyl)), 134.75 (C2), 137.13 (C4′ (phenyl)), 141.08 (C1′ (phenyl)). All measured values were identical to those in the literature.[16]

Typical Procedure for the Synthesis of 1,2-Epoxy-4-alkanols (2). A solution of *m*-CPBA (14.8 g, 70%, 0.06 mol) in CH$_2$Cl$_2$ (80 mL) was added to a solution of homoallylic alcohol (**1a-f**) (0.05 mol) in CH$_2$Cl$_2$ (40 mL). The solution was stirred for 10 h at -5 ºC. The mixture was quenched with 10% aqueous NaOH solution and extracted by CH$_2$Cl$_2$. The combined extracts were washed with saturated aqueous Na$_2$SO$_3$ and brine, dried over anhydrous MgSO$_4$, and concentrated. The residue was distilled under reduced pressure or purified by column chromatography to afford 1,2-epoxy-4-alkanol (**2a-f**) as a colorless to light yellow oil.

1,2-Epoxypentan-4-ol (2a): the crude product was obtained in about 92% yield (4.7 g) and went to next step without further purification. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.23 (d, *J* = 6.0 Hz) and 1.24 (d, *J* = 6.3 Hz) (partly overlapping, 3 H, HC5), 1.45-1.64 (m, 1 H, HC3), 1.76-1.91 (m, 1 H, H′C3), 2.19 (br, 1 H, OH), 2.50 (dd, *J* = 5.1, 2.7 Hz, 0.56 H, *syn*-, HC1), 2.61 (dd, *J* = 4.8, 3.0 Hz, 0.44 H, *anti*-, HC1), 2.74-2.85 (m, 1 H, H′C1), 3.01-3.17 (m, 1 H, HC2), 3.94-4.16 (m, 1 H, HC4). ^{13}C NMR (75 MHz, CDCl$_3$): δ 23.31 (C5, *syn*-), 23.60 (C5, *anti*-), 41.40 (C-3, *syn*-), 40.99 (C-3, *anti*-), 46.64 (C-1, *syn*-), 46.92 (C-1, *anti*-), 50.33 (C-2, *syn*-), 50.11 (C-2, *anti*-), 66.10 (C-4, *syn*-), 65.28 (C-4, *anti*-). All measured values were identical to those in the literature.[17]

1,2-Epoxydecan-4-ol (2b): the crude product was obtained in about 7.2 g (93%) yield and went to next step without further purification. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.88 (t, *J* = 6.9 Hz, 3 H, Me), 1.20-1.39 (m, 8 H, HC6~HC9), 1.40-1.66 (m, 3 H, HC5 and HC3), 1.77-1.91 (m, 1 H, H′C3), 2.08 (br. S, 1 H, -OH), 2.51 (dd, *J* = 4.8, 2.7 Hz, 0.55 H, HC1), 2.62 (dd, *J* = 4.8, 2.7 Hz, 0.45 H, HC1), 2.79 (t, *J* = 4.8 Hz, 0.55 H, H′C1), 2.83 (t, *J* = 4.8 Hz, 0.45 H, H′C1), 3.01-3.17 (m, 1 H, HC2), 3.94-4.16 (m, 1 H, HC4). ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.75 (Me), 22.31 (C9), 25.24 and 25.27 (C6), 29.02 (C7), 31.53 (C8), 37.11 and 37.40 (C5), 39.33 and 39.52 (C3), 46.35 and 46.87 (C1), 49.96 and 50.17 (C2), 68.79 and 69.69 (C4). All measured values were identical to those in the literature.[18]

1,2-Epoxy-5-methylhexan-4-ol (2c): colorless oil; yield: 6.1 g (94%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.87-0.89 (d, *J* = 6.9 Hz, 6 H, HC6), 1.42-1.55 (m, 1 H, HC3), 1.59-1.80 (m, 2 H, HC5 and HC3), 2.36

(s, 1 H, -OH), 2.46 (dd, J = 4.8, 3.0 Hz, 0.5 H, HC1), 2.57 (dd, J = 4.8, 3.0 Hz, 0.5 H, HC1), 2.74 (t, J = 4.2 Hz, 0.5 H, HC1), 2.79 (t, J = 4.2 Hz, 0.5 H, HC1), 3.03-3.14 (m, 1 H, HC2), 3.53-3.59 (m, 1 H, HC4). ^{13}C NMR (75 MHz, CDCl$_3$): δ 17.32 (C6), 18.38 and 18.49 (C6), 33.62 and 33.77 (C5), 36.06 and 36.46 (C3), 46.56 and 47.16 (C1), 50.58 and 51.12 (C2), 73.76 and 75.16 (C4). All measured values were identical to those in the literature.[19]

1,2-Epoxy-5,5-dimethylhexan-4-ol (2d): colorless oil; yield: 6.7 g (93%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.89 (s, 9 H, HC6), 1.33-1.44 (m, 0.5 H, HC3), 1.56 (dd, J = 6.3, 1.8 Hz, 0.5 H, HC3), 1.67-1.77 (m, 0.5 H, HC3), 1.87 (ddd, J = 14.4, 4.2, 1.8 Hz, 0.5 H, HC3), 2.11 and 2.25 (s, 1 H, -OH), 2.49 (dd, J = 4.8, 3.0 Hz, 0.5 H, HC1), 2.63 (dd, J = 4.8, 3.0 Hz, 0.5 H, HC1), 2.78 (t, J = 4.8 Hz, 0.5 H, HC1), 2.84 (t, J = 4.8 Hz, 0.5 H, HC1), 3.08-3.14 (m, 0.5 H, HC2), 3.16-3.22 (m, 0.5 H, HC2), 3.48 (t, J = 11.4 Hz, 1 H, HC4). ^{13}C NMR (75 MHz, CDCl$_3$): δ 25.45 and 25.47 (C6), 33.61 and 34.32 (C3), 34.62 and 34.66 (C5), 47.32 and 46.44 (C1), 51.03 and 51.89 (C2), 78.51 (C4). All measured values were identical to those in the literature.[19]

1,2-Epoxy-4-phenylbutan-4-ol (2e): light yellow oil; yield: 7.3 g (89%); bp 82-84 °C /0.05 kPa. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.26 (br, 1 H, -OH), 1.45-1.64 (m, 1 H, HC3), 1.77-1.91 (m, 1 H, HC3), 2.50 (dd, J = 4.8, 2.7 Hz, 0.5 H, HC1), 2.60 (dd, J = 4.8, 2.7 Hz, 0.5 H, HC1), 2.75 (t, J = 4.8 Hz, 0.5 H, HC1), 2.82 (t, J = 4.8 Hz, 0.5 H, HC1), 3.00 (m, 0.5 H, HC2), 3.17 (m, 0.5 H, HC2), 4.94 (m, 1 H, HC4), 7.26-7.41 (m, 5 H, phenyl). ^{13}C NMR (75 MHz, CDCl$_3$): δ 41.62 and 41.71 (C3), 46.92 and 47.34 (C1), 50.24 and 50.98 (C2), 71.56 and 72.35 (C4), 125.64 and 125.89 (C2′ and C6′ (phenyl)), 127.55 and 127.71 (C4′ (phenyl)), 128.47 and 128.51 (C3′ and C5′ (phenyl)), 143.92 and 144.28 (C1′ (phenyl)). All measured values were identical to those in the literature.[20]

1,2-Epoxy-4-*p*-methylphenylbutan-4-ol (2f): light yellow oil; yield: 8.1 g (91%); bp 103-105 °C /0.03 kPa. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.78 (ddd, J = 14.4, 6.9, 3.9 Hz, 0.5 H, HC3), 1.93 (m, 0.5 H, HC3), 2.02 (m, 0.5 H, HC3), 2.12 (ddd, J = 14.4, 9.0, 4.2 Hz, 0.5 H, HC3), 2.36 (s, 3 H, Me), 2.50 (br, 1 H, -OH), 2.50 (dd, J = 4.8, 2.7 Hz, 0.5 H, HC1, partly overlapping with the peak of -OH), 2.60 (dd, J = 4.5, 2.7 Hz, 0.5 H, HC1), 2.75 (t, J = 4.8 Hz, 0.5 H, HC1), 2.82 (t, J = 4.5 Hz, 0.5 H, HC1), 2.99 (m, 0.5 H, HC2), 3.16 (m, 0.5 H, HC2), 4.91 (m, 1 H, HC4), 7.13-7.21 (m, 2 H, HC3′ and HC5′ (phenyl)), 7.23-7.31 (m, 2 H, HC2′ and HC6′ (phenyl)). ^{13}C NMR (75 MHz, CDCl$_3$): δ 21.14 (Me), 41.47 and 41.75 (C3), 46.86 and 47.20 (C1), 50.07 and 50.29 (C2), 71.53 and 72.42 (C4), 125.58 and 125.79 (C2′ and C6′ (phenyl)), 129.18 and 129.21 (C3′ and C5′ (phenyl)), 137.26 and 137.42 (C4′ (phenyl)), 140.92 and 141.22 (C1′ (phenyl)). HRMS (ESI): m/z [M+Na$^+$] calcd for C$_{11}$H$_{14}$NaO$_2$, 201.088600; found: 201.088704.

Typical Procedure for the Synthesis of 1,2-Epoxy-4-alkanyl Mesylate (3). 1,2-Epoxy-alkan-4-ol (**2a-f**) (20 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and cooled to 0 °C. Triethylamine (5.6 mL, 40 mmol) and methanesulfonyl chloride (2.3 mL, 30 mmol) were slowly added at 0-5 °C successively. After stirring at room temperature for 12 h, the reaction mixture was acidified by addition of 5% HCl solution at 0-5 °C. The reaction mixture was then extracted with CH_2Cl_2, and the combined organic phases were washed with saturated aqueous $NaHCO_3$ solution and brine successively, dried over $MgSO_4$, and concentrated under reduced pressure. After concentration, the residue was submitted to column chromatography (petroleum ether/EtOAc, 6:1) to give **3a-f** as light yellow oil.

1,2-Epoxypentan-4-yl mesylate (3a): light yellow oil; yield: 3.7 g (76%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.50 (d, J = 6.3 Hz, 1.5 H, HC5), 1.52 (d, J = 6.3 Hz, 1.5 H, HC5), 1.64 (ddd, J = 14.7, 7.5, 2.7 Hz, 0.5 H, HC3), 1.77-1.89 (m, 0.5 H, HC3), 1.95-2.13 (m, 1 H, H'C3), 2.51 (dd, J = 4.8, 2.7 Hz, 0.5 H, HC1), 2.54 (dd, J = 4.8, 2.4 Hz, 0.5 H, HC1), 2.80 (dd, J = 4.8, 4.2 Hz, 0.5 H, H'C1), 2.85 (dd, J = 4.8, 4.2 Hz, 0.5 H, H'C1), 3.04 (s, 3 H, Me (mesyl)), 3.05 (m, 1 H, HC2) (partly overlapping with Me of mesyl group), 5.01 (m, 1 H, HC4). ^{13}C NMR (75 MHz, CDCl$_3$): δ 21.07 and 21.59 (C5), 38.30 and 38.48 (C3), 39.36 and 39.62 (Me (mesyl)), 46.13 and 47.26 (C1), 48.48 (C2), 77.69 (C4). HRMS (ESI): m/z [M+Na$^+$] calcd for C$_6$H$_{12}$NaO$_4$S, 203.034851; found: 203.034890.

1,2-Epoxydecan-4-yl mesylate (3b): light yellow oil; yield: 4.0 g (78%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.88 (t, J = 6.9 Hz, 3 H, Me), 1.30-1.51 (m, 8 H, HC6~HC9), 1.67-1.88 (m, 3 H, HC3 and HC5), 1.96-2.14 (m, 1 H, H'C3), 2.50 (dd, J = 4.5, 2.7 Hz, 0.55 H, HC1), 2.53 (dd, J = 4.8, 2.4 Hz, 0.45 H, HC1), 2.80 (t, J = 4.5 Hz, 0.55 H, H'C1), 2.84 (t, J = 4.8 Hz, 0.45 H, H'C1) 3.04 and 3.05 (s, 3 H, Me (mesyl), 3.05 (m, 1 H, HC2, partly overlapping with the peaks of Me of mesyl group), 4.88 (m, 1 H, HC4). ^{13}C NMR (75 MHz, CDCl$_3$): δ 13.72 (Me), 22.21 (C9), 24.48 and 24.77 (C6), 28.59 and 28.62 (C7), 31.26 (C8), 34.28 and 34.82 (C5), 37.42 and 37.46 (C3), 38.12 and 38.26 (Me (mesyl)), 45.86 and 47.05 (C1), 48.23 and 48.32 (C2), 80.96 and 81.05 (C4). HRMS (ESI): m/z [M+Na$^+$] calcd for C$_{11}$H$_{22}$NaO$_4$S, 273.113101; found: 273.113041.

1,2-Epoxy-5-methylhexan-4-yl mesylate (3c): light yellow oil; yield: 3.31 g (79%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.00 and 0.98 (d, J = 6 Hz, partly overlapping, 6 H, HC6), 1.64-1.72 (m, 0.5 H, HC3), 1.77-1.89 (m, 0.5 H, HC3), 1.93-2.03 (m, 1 H, H'C3), 2.04-2.13 (m, 1 H, HC5), 2.48 (dd, J = 4.8, 2.7 Hz, 0.5 H, HC1), 2.54 (dd, J = 4.8, 2.7 Hz, 0.5 H, HC1), 2.78 (dd, J = 4.8, 4.2 Hz, 0.5 H, H'C1), 2.84 (dd, J = 4.8, 4.2 Hz, 0.5 H, H'C1), 3.03-3.05 (m, 4 H, Me (mesyl) and HC2, all overlapping with Me of mesyl group), 5.01 (m, 1 H, HC4). ^{13}C NMR (75 Hz, CDCl$_3$): δ 17.74 and 18.06 (C6), 31.90 and 32.12 (C5), 34.15 and 34.74 (C3), 38.51 and 38.71 (Me (mesyl)), 46.22 and 47.64 (C1), 48.94 and 49.01 (C2), 85.22

and 85.68 (C4). HRMS (ESI): *m/z* [M+Na$^+$] calcd for C$_8$H$_{16}$NaO$_4$S, 231.066232; found: 231.066151.

1,2-Epoxy-5,5-dimethylhexan-4-yl mesylate (3d): light yellow oil; yield: 3.20 g (72%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.98 (s, 9 H, HC6), 1.67-1.77 (m, 0.5 H, H′C3), 1.85 (t, *J* = 5.7 Hz, 0.5 H, H′C3), 1.98 (t, *J* = 2.7 Hz, 0.5 H, HC3), 2.03 (t, *J* = 2.7 Hz, 0.5 H, HC3), 2.46 (dd, *J* = 4.8, 2.7 Hz, 0.5 H, H′C1), 2.55 (dd, *J* = 4.8, 2.7 Hz, 0.5 H, H′C1), 2.79 (t, *J* = 4.2 Hz, 0.5 H, HC1), 2.86 (t, *J* = 4.2 Hz, 0.5 H, HC1), 3.03-3.13 (m, 4 H, Me (mesyl) and HC2, partly overlapping with mesyl group), 4.66-4.68 (m, 1 H, HC4). ^{13}C NMR (75 MHz, CDCl$_3$): δ 25.9 (C6), 34.08 and 34.14 (C3), 34.77 and 34.89 (C5), 38.65 and 39.00 (Me (mesyl)), 46.11 and 48.35 (C1), 49.55 and 49.95 (C2), 88.16 and 88.75 (C4). HRMS (ESI): *m/z* [M+Na$^+$] calcd for C$_9$H$_{18}$NaO$_4$S, 245.081842; found: 245.081801.

1,2-Epoxy-4-phenylbutan-4-yl mesylate (3e): light yellow oil; yield: 3.7 g (76%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.93 (ddd, *J* = 14.7, 6.9, 3.9 Hz, 0.5 H, HC3), 2.17 (m, 0.5 H, HC3), 2.26-2.43 (m, 1 H, HC3), 2.52 (dd, *J* = 4.8, 2.7 Hz, 0.5 H, HC1), 2.57 (dd, *J* = 4.8, 2.4 Hz, 0.5 H, HC1), 2.75 (t, *J* = 4.8 Hz, 0.5 H, HC1), 2.87 (t, *J* = 4.8 Hz, 0.5 H, HC1), 2.70 and 2.72 (s, 3 H, Me (mesyl)), 2.88 (m, 0.5 H, HC2), 3.15 (m, 0.5 H, HC2), 5.75 (m, 1 H), 7.39-7.48 (m, 5 H, phenyl). ^{13}C NMR (300 MHz, CDCl$_3$): δ 39.02 and 39.11 (Me (mesyl)), 40.01 and 40.47 (C3), 46.72 and 47.49 (C1), 48.57 and 48.65 (C2), 82.15 and 82.23 (C4), 126.56 and 126.82 (C2′ and C6′ (phenyl)), 129.08 and 129.12 (C3′ and C5′ (phenyl)), 129.40 and 129.50 (C4′ (phenyl)), 137.43 and 137.88 (C1′ (phenyl)). The HRMS was not obtained due to its unstability.

1,2-Epoxy-4-*p*-methylphenyl-butan-4-yl mesylate (3f): light yellow oil; yield: 4.0 g (78%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.88 (ddd, *J* = 14.4, 6.9, 4.2 Hz, 0.5 H, HC3), 2.12 (m, 0.5 H, HC3), 2.25 (m, 1 H, HC3), 2.32 and 2.33 (s, 3 H, Me (phenyl)), 2.46 (dd, *J* = 4.8, 2.7 Hz, 0.5 H, HC1), 2.51 (dd, *J* = 5.1, 2.7 Hz, 0.5 H, HC1), 2.65 and 2.66 (s, 3 H, Me (mesyl)), 2.67 (m, 0.5 H, HC1), 2.81 (m, 0.5 H, HC1), 3.07 (m, 1 H, HC2), 5.65 (m, 1 H, HC4), 7.19 (m, 2 H, HC3′ and HC5′ (phenyl)), 7.29 (m, 2 H, HC2′ and HC6′ (phenyl)). ^{13}C NMR (75 MHz, CDCl$_3$): δ 21.16 (Me (phenyl)), 38.91 and 38.98 (Me (mesyl)), 39.88 and 40.28 (C3), 46.20 and 46.56 (C1), 48.56 and 48.60 (C2), 82.22 (C4), 126.56 and 126.79 (C2′ and C6′ (phenyl)), 129.64 and 129.69 (C3′ and C5′ (phenyl)), 134.46 and 134.91 (C4′ (phenyl)), 139.24 and 139.34 (C1′ (phenyl)). The HRMS was not obtained due to its unstability.

Typical Procedure for the Synthesis of Products 4, 5 and 10. To a mixture of anhydrous potassium carbonate (5.5 g, 40 mmol), absolute MeCN (100 mL) and 18-crown-6 (0.26 g, 1 mmol) was added thioacetic acid (2.0 mL, 28 mmol). The mixture was stirred at room temperature for 15 min and 1,2-epoxy-4-alkanyl mesylate (**3a-f**) (20 mmol) was added. After the addition, the mixture was heated at reflux for 12 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was acidified with 5% aqueous HCl, and then extracted with Et$_2$O. The combined organic layers were washed with

saturated aqueous NaHCO₃ solution and brine successively and dried over MgSO₄. After concentration under vacuum, the residue was submitted to column chromatography (petroleum ether/ EtOAc, 50:1). **3a-d** gave *cis-* and *trans-*isomers of **4a-d** separately as a light yellow oil, whereas **3e** and **3f** (2.4 eq. AcSH) gave 1,4-diacetylthio-4-phenylbut-2-yl acetate (**5a**) and 1,4-diacetylthio-4-*p*-methylphenylbut-2-yl acetate (**5b**) respectively.

2-Methyl-4-acetoxytetrahydrothiophene (4a). The *cis-* and *trans-*mixture were produced in about 81% yield (2.6 g). It was difficult to separate these two isomers and only a little amount of pure isomers were obtained for NMR and HRMS analyses. ***cis-*Isomer 4a:** ^{1}H NMR (300MHz, CDCl₃): δ 1.40 (d, J = 6.6 Hz, 3 H, MeC2), 1.80 (dt, J = 13.8, 7.2 Hz, 1 H, HC3), 2.08 (s, 3 H, MeC=O), 2.41 (m, 1 H, H′C3), 2.97 (dd, J = 10.8, 5.4 Hz, 1 H, HC5), 3.18 (dd, J = 10.8, 6.0 Hz, 1 H, H′C5), 3.52 (m, 1 H, HC2), 5.34 (m, 1 H, HC4). ^{13}C NMR (75 MHz, CDCl₃): δ 21.12 (MeC=O), 23.14 (MeC2), 36.41 (C5), 39.52 (C2), 43.00 (C3), 76.82 (C4), 170.50 (C=O). HRMS (ESI): m/z [M+Na$^+$] calcd for C₇H₁₂NaO₂S, 183.045021; found: 183.044998. ***trans-*Isomer 4a:** ^{1}H NMR (300 MHz, CDCl₃): δ 1.40 (d, J = 6.6 Hz, 3 H, MeC2), 1.68 (ddd, J = 13.8, 10.2, 3.6 Hz, 1 H, HC3), 2.08 (s, 3 H, MeC=O), 2.31 (dd, J = 13.8, 4.8 Hz, 1 H, H′C3), 2.95 (d, J = 12.6 Hz, 1 H, HC5), 3.32 (dd, J = 12.6, 5.4 Hz, 1 H, H′C5), 3.68 (m, 1 H, HC2), 5.52 (m, 1 H, HC4). ^{13}C NMR (75 MHz, CDCl₃): δ 21.07 (MeC2), 21.26 (MeC=O), 38.03 (C5), 41.12 (C2), 44.57 (C3), 77.47 (C4), 170.55 (C=O). HRMS (ESI): m/z [M+Na$^+$] calcd for C₇H₁₂NaO₂S, 183.045021; found: 183.045004. **2-Hexyl-4-acetoxytetrahydrothiophene (4b).** ***cis-*Isomer 4b:** light yellow oil; yield: 1.8 g (39%). ^{1}H NMR (600 MHz, CDCl₃): δ 0.87 (t, J = 7.2 Hz, 3 H, Me (hexyl)), 1.21-1.40 (m, 8 H, HC2′~HC5′ (hexyl)), 1.60 (m, 1 H, HC1′ (hexyl)), 1.69 (m, 1 H, H′C1′ (hexyl)), 1.77 (dt, J = 15.0, 7.2 Hz, 1 H, HC3), 2.05 (s, 3 H, Me (acetyl)), 2.38 (m, 1 H, H′C3), 2.86 (dd, J = 11.4, 6.0 Hz, 1 H, HC5), 3.12 (dd, J = 11.4, 6.6 Hz, 1 H, H′C5), 3.34 (m, 1 H, HC2), 5.28 (m, 1 H, HC4). ^{13}C NMR (150 MHz, CDCl₃): δ 14.03 (Me (hexyl)), 21.10 (Me (acetyl)), 22.55 (C5′ (hexyl)), 28.66 (C3′ (hexyl)), 29.04 (C2′ (hexyl)), 31.69 (C4′ (hexyl)), 35.31 (C5), 37.91 (C1′ (hexyl)), 41.04 (C3), 45.07 (C2), 76.49 (C4), 170.44 (C=O). HRMS (ESI): m/z [M+Na$^+$] calcd for C₁₂H₂₂NaO₂S, 253.123272; found: 253.123087. ***trans-*Isomer 4b:** light yellow oil; yield: 2.0 g (43%). ^{1}H NMR (600 MHz, CDCl₃): δ 0.83 (t, J = 6.6 Hz, 3 H, Me (hexyl)), 1.23-1.32 (m, 8 H, HC2′~HC5′ (hexyl)), 1.53 (m, 1 H, HC1′ (hexyl)), 1.60 (m, 1 H, HC3), 1.66 (m, 1 H, H′C1′ (hexyl)), 2.01 (s, 3 H, Me (acetyl)), 2.24 (d, J = 13.8 Hz, 1 H, H′C3), 2.85 (d, J = 12.0 Hz, 1 H, HC5), 3.16 (dd, J = 12.0, 4.8 Hz, 1 H, H′C5), 3.49 (m, 1 H, HC2), 5.43 (m, 1 H, HC4). ^{13}C NMR (150 MHz, CDCl₃): δ 14.01 (Me (hexyl)), 21.16 (Me (acetyl)), 22.52 (C5′ (hexyl)), 29.13 (C3′ (hexyl)), 29.22 (C2′ (hexyl)), 31.64 (C4′ (hexyl)), 36.62 (C1′ (hexyl)), 36.99 (C5), 42.50 (C3), 46.97 (C2), 77.13 (C4), 170.38 (C=O). HRMS (ESI): m/z [M+Na$^+$] calcd for C₁₂H₂₂NaO₂S, 253.123272; found: 253.123104.

2-*i*-Propyl-4-acetoxytetrahydrothiophene (4c). *cis*-**Isomer 4c:** light yellow oil; yield: 1.3 g (35%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.94 and 0.96 (d, J = 6.0 Hz, 6 H, Me (*i*-Propyl), partly overlapping), 1.67-1.77 (m, 2 H, HC3 and CH (*i*-Propyl)), 2.03 (s, 3 H, Me (acetyl)), 2.35-2.43 (m, 1 H, HC3), 2.78 (dd, J = 10.8, 7.8 Hz, 1 H, HC5), 3.08-3.13 (m, 2 H, HC5 and HC2, partly overlapping), 5.16-5.26 (m, 1 H, HC4). ^{13}C NMR (75 MHz, CDCl$_3$): δ 20.90 and 21.43 (Me (*i*-Propyl)), 21.10 (Me (acetyl)), 34.58 (C5), 34.94 (CH (*i*-Propyl)), 38.53 (C3), 51.79 (C2), 76.29 (C4), 170.55 (C=O). HRMS (ESI): *m/z* [M+Na$^+$] calcd for C$_9$H$_{16}$NaO$_2$S, 211.076321; found: 211.076337. *trans*-**Isomer 4c:** light yellow oil; yield: 1.2 g (31%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.98 and 1.01 (d, J = 6.0 Hz, 6 H, Me (*i*-Propyl), partly overlapping), 1.61-1.80 (m, 2 H, HC3 and CH(*i*-Propyl)), 2.07 (s, 3 H, Me (acetyl)), 2.26 (dd, 1 H, J = 13.5, 5.4 Hz, HC3), 2.92 (d, 1 H, J = 12.3 Hz, HC5), 3.17 (dd, 1 H, J = 12.3, 4.5 Hz, HC5), 3.33-3.41 (m, 1 H, HC2), 5.50 (s, 1 H, HC4). ^{13}C NMR (75 MHz, CDCl$_3$): δ 21.29 (Me (*i*-Propyl)), 22.18 (Me (acetyl)), 34.41 (CH (*i*-Propyl)), 37.10 (C5), 40.33 (C3), 54.78 (C2), 77.60 (C4), 170.60 (C=O). HRMS (ESI): *m/z* [M+Na$^+$] calcd for C$_9$H$_{16}$NaO$_2$S, 211.076321; found: 211.076328.

2-*t*-Butyl-4-acetoxytetrahydrothiophene (4d). *cis*-**Isomer 4d:** light yellow oil; yield: 1.4 g (34%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.95 (s, 9 H, Me (*t*-Butyl)), 1.58-1.70 (m, 1 H, HC3), 2.05 (s, 3 H, Me (acetyl)), 2.30-2.38 (m, 1 H, HC3), 2.70 (t, J = 9.3 Hz, 1 H, HC5), 3.07 (dd, J = 10.5, 6.6 Hz, 1 H, HC5), 3.30 (dd, J = 10.8, 6.6 Hz, 1 H, HC2), 5.13-5.23 (m, 1 H, HC4). ^{13}C NMR (75 MHz, CDCl$_3$): δ 21.11 (Me (acetyl)), 27.10 (Me (*t*-Butyl)), 33.78 (C (*t*-Butyl)), 34.13 (C5), 35.28 (C3), 55.10 (C2), 76.13 (C4), 170.61 (C=O). HRMS (ESI): *m/z* [M+Na$^+$] calcd for C$_{10}$H$_{18}$NaO$_2$S, 225.091972; found: 225.091918. *trans*-**Isomer 4d:** light yellow oil; yield: 1.2 g (31%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.98 (s, 9 H, Me (*t*-Butyl)), 1.67-1.76 (m, 1 H, HC3), 2.05-2.15 (m, 4 H, Me (acetyl) and HC3), 2.91 (d, 1 H, J = 12.3 Hz, HC5), 3.11 (dd, 1 H, J = 12.6, 4.5 Hz, HC5), 3.57 (dd, 1 H, J = 11.1, 6.0 Hz, HC2), 5.49 (s, 1 H, HC4). ^{13}C NMR (75 MHz, CDCl$_3$): δ 21.35 (Me (acetyl)), 27.71 (Me (*t*-Butyl)), 33.44 (C (*t*-Butyl)), 37.05 (C5), 37.14 (C3), 58.88 (C2), 77.85 (C4), 170.70 (C=O). HRMS (ESI): *m/z* [M+Na$^+$] calcd for C$_{10}$H$_{18}$NaO$_2$S, 225.091972; found: 225.091949.

1,4-Diacetylthio-4-phenylbut-2-yl acetate (5a): light brown oil; yield: 2.9 g (42%). ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.94 and 2.03 (s, 3 H, Me (acetoxy)), 2.15-2.35 (m, 2 H, HC3), 2.28 and 2.29 (s, 3 H, Me (thioacetyl-C4), 2.32 and 2.34 (s, 3 H, Me (thioacetyl-C1)), 3.01 (dd, J = 14.4, 5.4 Hz, 0.45 H, HC1), 3.05 (dd, J = 13.8, 5.4 Hz, 0.55 H, HC1), 3.24 (dd, J = 14.4, 4.2 Hz, 0.45 H, HC1), 3.28 (dd, J = 13.8, 3.9 Hz, 0.55 H, HC1), 4.65 (dd, J = 9.6, 6.0 Hz, 0.45 H, HC4), 4.70 (t, J = 7.8 Hz, 0.55 H, HC4), 4.79 (m, 0.45 H, HC2), 5.11 (m, 0.55 H, HC2), 7.23-7.35 (m, 5 H, phenyl). ^{13}C NMR (150 MHz, CDCl$_3$): δ 20.83 and 20.93 (Me (acetoxy)), 30.39 and 30.41 (Me (thioacetyl-C4)), 30.47 and 30.49 (Me (thioacetyl-C1)), 32.40 and 32.49 (C1), 38.77 and 39.37 (C3), 44.24 and 44.33 (C4), 70.00 (C2), 127.52 and 127.68 (C2′ and C6′ (phenyl)), 127.58 and 127.75 (C4′ (phenyl)), 128.79 and 128.85 (C3′ and C5′ (phenyl)), 140.30 and

141.22 (C1′ (phenyl)), 170.14 and 170.28 (C=O (acetoxy)), 194.01 and 194.17 (C=O (thioacetyl-C4)), 194.38 and 194.49 (C=O (thioacetyl-C1)). HRMS (ESI): *m/z* [M+Na$^+$] calcd for C$_{16}$H$_{20}$NaO$_4$S$_2$:363.069522; found: 363.069199.

1,4-Diacetylthio-4-*p*-methylphenylbut-2-yl acetate (5b): light brown oil; yield: 2.7 g (38%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.94 and 2.03 (s, 3 H, Me (acetoxy)), 2.15-2.35 (m, 2 H, HC3), 2.27 and 2.28 (s, 3 H, Me (thioacetyl-C4), 2.30 and 2.31 (s, 3 H, Me (phenyl)), 2.32 and 2.33 (s, 3 H, Me (thioacetyl-C1)), 3.01 (dd, *J* = 12.6, 5.4 Hz, 0.5 H, HC1), 3.03 (dd, *J* = 14.4, 5.4 Hz, 0.5 H, HC1), 3.22 (dd, *J* = 12.6, 4.8 Hz, 0.5 H, HC1), 3.26 (dd, *J* = 14.4, 4.8 Hz, 0.5 H, HC1), 4.60 (dd, *J* = 10.2, 6.0 Hz, 0.5 H, HC4), 4.65 (dd, *J* = 9.0, 6.9 Hz, 0.5 H, HC4), 4.76 (m, 0.5 H, HC2), 5.07 (m, 0.5 H, HC2), 7.09-7.21 (m, 4 H, phenyl). ^{13}C NMR (75 MHz, CDCl$_3$): δ 20.84 and 20.94 (Me (acetoxy)), 21.10 (Me (phenyl)), 30.40 (Me (thioacetyl-C4)), 30.46 (Me (thioacetyl-C1)), 32.41 (C1), 38.76 and 39.36 (C3), 43.97 and 44.00 (C4), 69.99 and 70.02 (C2), 127.35 and 127.51 (C2′ and C6′ (phenyl)), 129.44 and 129.52 (C3′ and C5′ (phenyl)), 137.13 and 137.29 (C4′ (phenyl)), 137.45 and 138.11 (C1′ (phenyl)), 170.18 and 170.30 (C=O (acetoxy)), 194.16 and 194.34 (C=O (thioacetyl-C4), 194.44 and 194.55 (C=O (thioacetyl-C1). HRMS (ESI): *m/z* [M+Na$^+$] calcd for C$_{17}$H$_{22}$NaO$_4$S$_2$, 377.085172; found: 377.085262.

2-Methyl-5-acetoxy-6-acetylthio-2-hexene (6). It was obtained as a by-product in 21% yield when the substrate **3c** reacted with AcSH. ^{1}HNMR (300 MHz, CDCl$_3$): δ 1.60 (s, 3 H, Me), 1.69 (s, 3 H, HC1), 2.01 (s, 3 H, Me (acetylthio)), 2.26-2-32 (m, 5 H, Me (acetoxy) and HC4), 2.95 (dd, *J* = 13.5, 7.5 Hz, 1 H, HC6), 3.2 (dd, *J* = 13.5, 4.5 Hz, 1 H, HC6), 4.92 (m, 1 H, HC5), 5.06 (m, 1 H, HC3). ^{13}C NMR (75 MHz, CDCl$_3$): δ 17.88 (C1), 20.99 (Me (acetylthio)), 25.76 (Me), 30.45 (Me (acetoxy)), 31.93 (C6), 32.12 (C4), 72.32 (C5), 117.97 (C3), 135.40 (C2), 170.31 (C=O (acetoxy)), 194.74 (C=O (acetylthio)). HRMS (ESI): *m/z* [M+Na$^+$] calcd for C$_{11}$H$_{18}$NaO$_3$S, 253.086886; found: 253.086752.

1,2-Epoxy-4-phenylbutan-4-yl thioacetate (7): light yellow oil; yield: 1.5 g (34%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.09 (m, 0.43 H, HC3), 2.18 (m, 1.14 H, HC3), 2.26-2.39 (m, 0.43 H, HC3), 2.33 and 2.34 (s, 3 H, Me), 2.40 (dd, *J* = 4.8, 3.0 Hz, 0.57 H, HC1), 2.55 (dd, *J* = 4.8, 3.0 Hz, 0.43 H, HC1), 2.67 (t, *J* = 4.8 Hz, 0.57 H, HC1), 2.77 (t, *J* = 4.8 Hz, 0.43 H, HC1), 2.86 (m, 0.57 H, HC2), 2.95 (m, 0.43 H, HC2), 4.83 (m, 1 H, HC4), 7.26-7.41 (m, 5 H, phenyl). ^{13}C NMR (75 MHz, CDCl$_3$): δ 30.45 (Me (acetyl)), 39.37 and 39.56 (C3), 45.43 and 45.54 (C4), 47.11 and 47.25 (C1), 50.14 and 50.18 (C2), 127.53 (C4′ (phenyl)), 127.63 and 127.67 (C2′ and C6′ (phenyl)), 128.76 (C3′ and C5′ (phenyl)), 140.94 and 141.12 (C1′ (phenyl)), 194.16 and 194.22 (C=O). HRMS (ESI): *m/z* [M+Na$^+$] calcd for C$_{12}$H$_{14}$NaO$_2$S, 245.060671; found: 245.060583.

2-Phenyl-4-acetylthiotetrahydrothiophene (10a): light yellow oil; yield: 3.9 g (82%). ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.87 (q, *J* = 12.0 Hz, 0.5 H, HC3, isomer 1), 2.24 and 2.25 (s, 3 H, Me-C=O), 2.29 (m, 1

H, HC3, isomer 2), 2.63 (dt, J = 12.0, 5.7 Hz, 0.5 H, H′C3, isomer 1), 2.85 (dd, J = 11.4, 4.8 Hz, 0.5 H, HC5, isomer 2), 2.97 (t, J = 10.5 Hz, 0.5 H, HC5, isomer 1), 3.24 (dd, J = 10.5, 6.9 Hz, 0.5 H, H′C5, isomer 1), 3.50 (dd, J = 11.4, 5.7 Hz, 0.5 H, H′C5, isomer 2), 3.95 (ddd, J = 10.8, 6.9, 5.1 Hz, 0.5 H, HC4, isomer 1), 4.29 (m, 0.5 H, HC4, isomer 2), 4.50 (dd, J = 11.1, 5.7 Hz, 0.5 H, HC2, isomer 1), 4.54 (t, J = 7.8 Hz, 0.5 H, HC2, isomer 2), 7.10-7.18 (m, 1 H, HC4′ (phenyl)), 7.18-7.26 (m, 2 H, HC3′ and HC5′ (phenyl)), 7.28-7.36 (m, 2 H, HC2′ and HC6′ (phenyl)). ^{13}C NMR (150 MHz, CDCl$_3$): δ 30.68 and 30.79 (Me-C=O), 37.41 and 39.15 (C5), 44.85 and 46.77 (C4), 45.42 and 45.46 (C3), 50.65 and 50.92 (C2), 127.35 and 127.47 (C4′), 127.59 (C2′ and C6′), 128.57 (C3′and C5′), 141.26 and 141.97 (C1′), 195.13 and 195.32 (C=O). HRMS (ESI): m/z [M+H$^+$] calcd for C$_{12}$H$_{15}$OS$_2$, 239.055884; found: 239.055920.

2-p-Methylphenyl-4-acetylthiotetrahydrothiophene (10b): light yellow oil; yield: 3.8 g (80%). ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.87 (q, J = 6.3 Hz, 0.5 H, HC3, isomer 1), 2.24 (s, 3 H, Me-phenyl), 2.25 and 2.27 (s, 3 H, Me-C=O), 2.23-2.37 (m, 1 H, HC3, isomer 2), 2.61 (dt, J = 6.3, 3.0 Hz, 0.5 H, H′C3, isomer 1), 2.85 (dd, J = 5.7, 2.4 Hz, 0.5 H, HC5, isomer 2), 2.98 (t, J = 5.4 Hz, 0.5 H, HC5, isomer 1), 3.24 (dd, J = 5.4, 3.6 Hz, 0.5 H, H′C5, isomer 1), 3.51 (dd, J = 5.7, 3.0 Hz, 0.5 H, H′C5, isomer 2), 3.95 (m, 0.5 H, HC4, isomer 1), 4.31 (m, 0.5 H, HC4, isomer 2), 4.49 (dd, J = 5.7, 3.0 Hz, 0.5 H, HC2, isomer 1), 4.53 (t, J = 3.6 Hz, 0.5 H, HC2, isomer 2), 7.02-7.06 (m, HC3′ and HC5′, 2 H, (phenyl)), 7.19-7.24 (m, 2 H, HC2′ and HC6′ (phenyl)). ^{13}C NMR (150 MHz, CDCl$_3$): δ 20.97 (Me-phenyl), 30.58 and 30.70 (Me-C=O), 37.31 and 39.06 (C5), 44.74 and 46.69 (C4), 45.35 (C3), 50.34 and 50.60 (C2), 127.39 (C2′ and C6′), 129.16 (C3′and C5′), 136.94 and 137.08 (C4′), 138.06 and 138.82 (C1′), 195.05 and 195.24 (C=O). HRMS (ESI): m/z [M+Na$^+$] calcd for C$_{13}$H$_{16}$NaOS$_2$, 275.053478; found: 275.053554.

Synthesis of 1,2-epithio-4-phenyl-4-butanol (13). The following procedure was referred to our previous work.[21] To a suspension of 1,2-epoxy-4-phenyl-4-butanol (3e) (0.82 g, 5 mmol) and thiourea (0.46 g, 6 mmol) in dry THF (20 mL) was added Ti(Oi-Pr)$_4$ (1.86 mL, 6 mmol) at room temperature under nitrogen. After addition, thiourea gradually dissolved and a clear solution formed. The mixture was stirred for 4 h. The solution was then diluted with Et$_2$O (10 mL) and quenched with saturated aqueous NaHCO$_3$ solution. The resulting mixture was stirred vigorously for ca. 1 h as a white precipitate separated from solution. The mixture was filtered through a pad of celite, and the residue was washed thoroughly with Et$_2$O and CH$_2$Cl$_2$. The combined organic phases were then washed with water and brine and then dried over anhydrous MgSO$_4$. After solvent removal, the residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 10:1) to afford 1,2-epithio-4-phenyl-4-butanol (13) as a colorless oil in 84% yield (0.76 g). ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.65 (m, 0.5 H, HC3), 1.96 (m, 0.5 H, HC3), 2.11 and 2.12 (d, J = 6.0, 0.5 H, HC1), 2.19 (m, 1 H, HC3 and HC1), 2.35 (m, 0.5 H, HC3), 2.42 and 2.43 (d, J = 6 Hz, 0.5 H, HC1), 2.50 (s, 0.5 H, -OH), 2.54 and 2.55 (d, J = 6 Hz, 1 H, HC1 and -OH), 2.71 (m, 0.5 H, HC2),

3.09 (m, 0.5 H, HC2), 4.82 (m, 1 H, HC4), 7.28 (m, 1 H, HC4′ (phenyl)), 7.34 and 7.37 (m, 4 H, HC2′, HC3′, HC5′ and HC6′ (phenyl)). ^{13}C NMR (150 MHz, CDCl$_3$): δ 25.50 and 26.14 (C1), 32.20 and 33.03 (C2), 45.40 and 45.73 (C3), 74.30 and 74.56 (C4), 125.73 and 125.08 (C2′ and C6′), 127.76 and 127.99 (C4′), 128.58 and 128.65 (C3′ and C5′), 144.09 and 143.62 (C1′). HRMS (ESI): *m/z* [M+Na$^+$] calcd for C$_{10}$H$_{12}$NaOS, 203.050107; found: 203.050192.

Synthesis of 1,2-epithio-4-phenyl-4-butyl mesylate (14). The procedure was the same as that for 1,2-epoxy-4-phenyl-4-butyl mesylate. 1,2-Epithio-4-phenyl-4-butyl mesylate (**14**) was obtained as a colorless oil in 87% yield (0.67 g). ^{1}H NMR (600 MHz, CDCl$_3$): δ 1.84 (m, 0.5 H, HC3), 2.14 and 2.15 (d, *J* = 6.0 Hz, 0.5 H, HC1), 2.23 and 2.24 (d, *J* = 6.0 Hz, 0.5 H, HC1), 2.26-2.29 (m, 0.5 H, HC3), 2.37-2.41 (m, 0.5 H, HC3), 2.44 and 2.45 (d, *J* = 6.0 Hz, 0.5 H, HC1), 2.55-2.88 (m, 1.5 H, HC3, HC2 and HC1) , 2.68 and 2.70 (s, 3 H, Me), 3.04 (m, 0.5 H, HC2), 5.63 (dd, *J* = 6.0 and 6.0 Hz, 0.5 H, HC4), 5.68 (dd, *J* = 6.0 and 6.0 Hz, 0.5 H, HC4), 7.31-7.43 (m, 5 H, phenyl). ^{13}C NMR (150 MHz, CDCl$_3$): δ 25.20 and 25.91 (C1), 30.35 and 31.42 (C2), 38.97 (Me), 43.39 and 44.09 (C3), 83.88 and 84.60 (C4), 126.48 and 126.81 (C2′ and C6′), 128.93 and 129.00 (C3′ and C5′), 129.25 and 129.42 (C4′), 137.09 and 137.66 (C1′). HRMS (ESI): *m/z* [M+Na$^+$] calcd for C$_{11}$H$_{14}$NaO$_3$S$_2$, 281.027657; found: 281.027809.

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REFERENCES

1. J. Zempleni, S. S. K. Wijeratne, and Y. I. Hassan, *Biofactors*, 2009, **35**, 36.
2. (a) M. F. Jones, S. A. Noble, C. A. Robertson, and R. Storer, *Tetrahedron Lett.*, 1991, **32**, 247; (b) M. F. Jones, S. A. Noble, C. A. Robertson, R. Storer, R. M. Highcock, and R. B. Lamont, *J. Chem. Soc., Perkin Trans.1*, 1992, 1427.
3. M. E. Jung and O. Kretschik, *J. Org. Chem.*, 1998, **63**, 2975.
4. K. Yamada, S. Sakata, and Y. Yoshimura, *J. Org. Chem.*, 1998, **63**, 6891.
5. (a) M. Yoshikawa, T. Murakami, H. Shimada, H. Matsuda, J. Yamahara, G. Tanabe, and O. Muraoka, *Tetrahedron Lett.*, 1997, **38**, 8367; (b) M. Yoshikawa, T. Morikawa, H. Matsuda, G. Tanabe, and O. Muraoka, *Bioorg. Med. Chem.*, 2002, **10**, 1547; (c) M. Yoshikawa, T. Murakami, K. Yashiro, and H. Matsuda, *Chem. Pharm. Bull.*, 1998, **46**, 1339; (d) M. Yoshikawa, F. Xu, S. Nakamura, T. Wang, H. Matsuda, G. Tanabe, and O. Muraoka, *Heterocycles*, 2008, **75**, 1397; (e) G. Tanabe, M. Sakano, T.

Minematsu, H. Matusda, M. Yoshikawa, and O. Muraoka, *Tetrahedron*, 2008, **64**, 10080.

6. A. K. Ghosh, H. Y. Lee, W. J. Thompson, C. Culberson, M. K. Holloway, S. P. McKee, P. M. Munson, T. T. Duong, A. M. Smith, P. L. Darke, J. A. Zugay, E. A. Emini, W. A. Schleif, J. R. Huffa, and P. S. Anderson, *J. Med. Chem.*, 1994, **37**, 1177.

7. C. J. O'Connor, M. D. Roydhouse, A. M. Przybył, M. D. Wall, and J. M. Southern, *J. Org. Chem.*, 2010, **75**, 2534.

8. (a) S. Benetti, C. De Risi, G. P. Pollini, and V. Zanirato, *Chem. Rev.*, 2012, **112**, 2129; (b) B. Mandal, S. Nandi, and S. C. Pan, *Eur. J. Org. Chem.*, 2017, **32**, 4666.

9. (a) M. Borah, P. Gogoi, K. Indukuri, and A. K. Saikia, *J. Org. Chem.*, 2015, **80**, 2641; (b) C. Xu, J. Du, L. Ma, G. Li, M. Tao, and W. Zhang, *Tetrahedron*, 2013, **69**, 4749; (c) A. M. Ponce and L. E. Overman, *J. Am. Chem. Soc.*, 2000, **122**, 8672.

10. B. Ma, S. Yang, F. Tao, B. Sun, Y. Liu, and H. Tian, *J. Chem. Res.*, 2015, **39**, 724.

11. M. Wolberg, B. H. N. Dassen, M. Schürmann, S. Jennewein, M. G. Wubbolts, H. E. Schoemaker, and D. Mink, *Adv. Synth. Catal.*, 2008, **350**, 1751.

12. G. Wang, L. Peng, Y. Zheng, Y. Gao, X. Wu, T. Ren, C. Gao, and J. Han, *RSC Adv.*, 2015, **5**, 5674.

13. Y.-G. Liu, X.-Q. Gong, H.-Y. Tian, and B.-G. Sun, *J. Chem. Res.*, 2012, **36**, 333.

14. G. J. Sormunen and D. E. Lewis, *Synth. Commun.*, 2004, **34**, 3473.

15. S. E. Denmark and S. T. Nguyen, *Org. Lett.*, 2009, **11**, 781.

16. L.-W. Ye, X.-L. Sun, C.-Y. Li, and Y. Tang, *J. Org. Chem.*, 2007, **72**, 1335.

17. L. D'Accolti, C. Fusco, C. Annese, M. R. Rella, J. S. Turteltaub, P. G. Williard, and R. Curci, *J. Org. Chem.*, 2004, **69**, 8510.

18. M. V. Chirskaya, A. A. Vasil'ev, S. V. Shorshnev, and S. I. Sviridov, *Russ. Chem. Bull., Int. Ed.*, 2006, **55**, 1300.

19. T. Biftu, D. Feng, G. Liang, M. Ponpipom, X. Qian, M. Fisher, M. Wyvratt, and R. Bugianesi, WO 2001034632, 2001.

20. B. Banerjee and S. C. Roy, *J. Org. Chem.*, 2006, 489.

21. S. Liang, B. Sun, S. Yang, Y. Liu, H. Tian, Y. Liu, and H. Chen, *J. Chem. Res.*, 2014, **38**, 343.