A fortuitously straightforward synthesis of 4-acetoxy-2-propyltetrahydrothiophene

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4-Acetoxy-2-propyltetrahydrothiophene was synthesised from 1-hepten-4-ol by a three-step route involving epoxidation and mesylation to 1,2-epoxy-4-heptyl mesylate and then reaction with thioacetate. An acetoxylated cyclic product was formed instead of the expected thioacetate, and a mechanism for its formation using an intramolecular transesterification is proposed.

Keywords: 1-hepten-4-ol, 1,2-epoxy-4-heptanol, 1,2-epoxy-4-heptyl mesylate, 4-acetoxy-2-propyltetrahydrothiophene, thioacetate

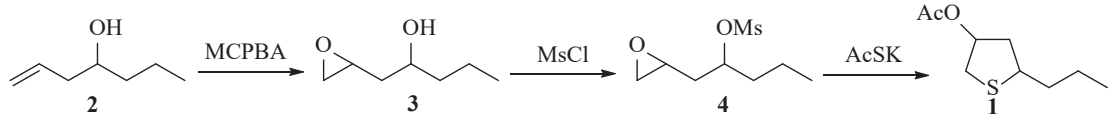
Tetrahydrothiophenes occur widely as important building blocks of many biologically active molecules, such as 3′-hetero-dideoxy nucleoside analogues as potential anti-HIV agents,[1,2] modified dideoxy isonucleosides with antiviral activity,[3] the essential coenzyme biotin as a water-soluble vitamin with important biological functions,[4] so do their derivatives, such as the corresponding cyclic sulfonium salts, the potent α-glucosidase inhibitors salacinol,[5,6] kotalanol,[7] salaprinol and ponkoranol[8,9] isolated from several *Salacia* plant species, and the related cyclic sulfolanes as high-affinity P_2 ligands for HIV-1 protease inhibitors.[10] A comprehensive review about the methods for the synthesis of tetrahydrothiophenes, provided by Benetti *et al*.,[11] included several different ways to produce chiral nonracemic tetrahydrothiophenes and some typical synthetic routes for the racemates. However, the available synthetic methods for both racemic and nonracemic tetrahydrothiophenes are still insufficient in view of the significance of tetrahydrothiophenes as basic scaffolds of many potential biologically active molecules and their versatilities in the field of applications.[12-15] More practically feasible routes with operational simplicity, high chemo- and regioselectivities and high yields awaited development.

In our present work concerning the synthesis of flavour compounds with 1,3-oxygen-sulfur functionality, the reaction of 1,2-epoxy-4-heptyl mesylate with thioacetic acid gave an unexpected product, 4-acetoxy-2-propyltetrahydrothiophene **1**. As far as we know, there are only a few methods reported in the literature to prepare such analogues. One of the analogues, nonracemic 5-[(benzyloxy)methyl]tetrahydrothiophen-3-ol was prepared by starting from diacetone-D-glucose through a 12-step route,[1,2] and the other one, 5-methyltetrahydrothiophene-3-ol was obtained by starting from ethyl 3-bromobutanoate and ethyl 2-mercaptoacetate through nucleophilic substitution, intramolecular Claisen condensation, hydrolysis and decarboxylation, and reduction.[10] In addition, 5-[(methoxycarbonyl)methylene]tetrahydrothiophen-3-ol was prepared by the reaction of δ-chloromethyl α,β-unsaturated δ-lactone with thioacetic acid followed by treatment with potassium carbonate.[16] Compared with these synthetic routes, the method we discovered fortuitously is more straightforward. We now show that 4-acetoxy-2-propyltetrahydrothiophene can be prepared easily by starting from 1-hepten-4-ol.

Results and discussion

Our three-step synthesis is shown in Scheme 1. 1-Hepten-4-ol **2**, prepared by the Grignard reaction of allylmagnesium chloride with *n*-butanal, was epoxidised with MCPBA to produce 1,2-epoxy-4-heptanol **3**, as previously described by us.[19] **3** was then reacted with MsCl to give 1,2-epoxy-4-heptyl mesylate **4**. The ^{1}H NMR spectra of epoxy alcohol **3** and its mesylate **4** showed that both of them were a mixture of diasteroisomers with a ratio of about 1/1. The original plan was that thioacetylation of mesylate **4** would be achieved by treatment with thioacetic acid in MeCN in the presence of potassium carbonate. However, the ^{13}C NMR spectrum of the crude product indicated that no thioacetyl group was present since there was not a signal at δ about 195, which is characteristic of the C=O of a thioacetyl group.[17,18] The unknown mixture was analysed by GC/MS which showed that it consisted of two major components in a ratio of about 1/1. It was tentatively deduced that the two major components were a pair of isomers based on the high similarity of their EI mass spectra. The two components were separated on a silica column with an effluent of petroleum ether/ethyl acetate, 50/1. ^{1}H and ^{13}C NMR spectra of both products indicated that the mesyl group and the epoxy group in the substrate **4** have disappeared. The signals at δ around 77 and 170 in the ^{13}C NMR spectrum and at δ around 5.4 in ^{1}H NMR spectrum demonstrated the possible presence of an ester group in the two products, although the signals at δ around 5.4 in the ^{1}H NMR spectrum appeared at a lower field than is used for the proton on a carbon attached directly to an acetoxy group.

In order to identify the structures of the two products, the two samples were analysed further using high resolution mass spectroscopy, DEPT, H,H- and H,C-correlation, and HMBC methods. Both products were identified to have the same molecular formula of $C_9H_{16}O_2S$ by high resolution mass spectroscopy. It could be concluded based on all the obtained data that the two products should be *cis*- and *trans*-4-acetoxy-



Scheme 1

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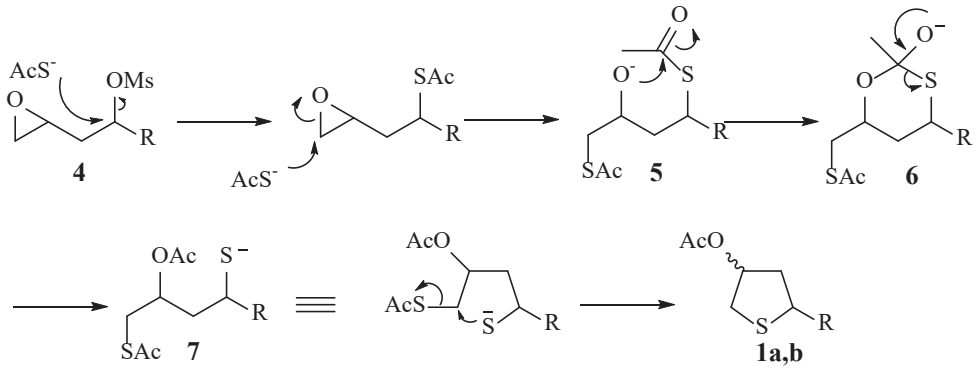
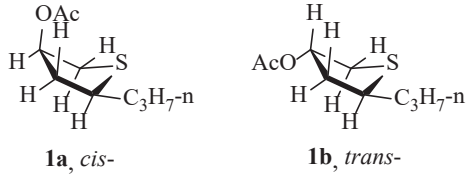


Scheme 2



1a, *cis*- **1b**, *trans*-

Fig. 1 *cis*- and *trans*-4-Acetoxy-2-propyltetrahydrothiophene.

2-propyltetrahydrothiophene **1a,b** respectively as shown in Fig. 1. The two isomers were analysed further by conducting NOE experiments with the irradiation of signal of H–C-2 or H–C-4. The results of NOE difference spectra permitted the assignment of the cis isomer (**1a**) and indicated that the signal of H–C-4 (δ 5.31) of the *cis*-isomer appeared at a relatively higher field than that (δ 5.50) of the *trans*-isomer (**1b**).

The proposed pathway of formation of **1a** and **1b** is shown in Scheme 2. The mesylate **4** suffered two successive nucleophilic substitutions by thioacetate to produce the intermediate **5**, which underwent an intramolecular transfer of an acetyl group through a six-membered cyclic intermediate **6** to give intermediate **7**. The final product, which was formed *via* an intramolecular nucleophilic displacement of a thioacetyl group by an alkylthio group in intermediate **7**, was a mixture of *cis*- and *trans*-4-acetoxy-2-propyltetrahydrothiophene **1a,b**.

We plan to extend the application of this efficient synthetic route to a wide range of homoallylic alcohols with different substituents to give novel disubstituted tetrahydrothiophenes. In addition, chiral non-racemic disubstituted tetrahydrothiophenes could easily be prepared using this route since the preparation of optically active homoallylic alcohols and asymmetric epoxidation can be achieved by many well-known methods.

Experimental

Allyl chloride (98%) and *m*-chloroperoxybenzoic acid (MCPBA, 70%) were purchased from Beijing Bailingwei Science and Technology Company (Beijing, China). The other chemicals and all solvents were purchased from Beijing Huaxue Shiji Company (Beijing, China). 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 spectra were obtained on a Bruker Apex IV FTMS.

1-Hepten-4-ol (**2**) *and 1,2-epoxy-4-heptanol* (**3**): Both prepared as previously described; the NMR data were consistent with those we have already reported.[19]

1,2-Epoxy-4-heptyl mesylate (**4**): 1,2-Epoxy-4-heptanol **3** (2.6 g, 20 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and cooled to 0 °C. Triethylamine (5.6 mL, 40 mmol) and methanesulfonylchloride (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 saturated brine successively, dried over $MgSO_4$, and concentrated under reduced pressure. After concentration, the residue was purified by column chromatography (petroleum ether/ethyl acetate, 6:1) to give **4** (3.8 g, 91% yield) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.94 (m, 3 H, H–C-7), 1.32–1.52 (m, 2 H, H–C-6), 1.64-1.86 (m, 3 H, H–C-3 and H–C-5), 1.98–2.11 (m, 1 H, H′–C-3), 2.48 (dd, *J* = 4.8, 2.7 Hz, 0.56 H, H–C-1, major diastereoisomer), 2.52 (dd, *J* = 5.1, 2.7 Hz, 0.44 H, H–C-1, minor diastereoisomer), 2.78 (t, *J* = 4.8 Hz, 0.56 H, H–C-1, major diastereoisomer), 2.83 (t, *J* = 5.1 Hz, 0.44 H, H–C-1, minor diastereoisomer), 3.00–3.10 (m, 4 H, H–C-2 and Me (mesyl)), 4.89 (m, 1 H, H–C-4); ^{13}C NMR ($CDCl_3$) δ 13.60 (C-7, major diastereoisomer), 13.64 (C-7, minor diastereoisomer), 18.05 (C-6, minor diastereoisomer), 18.33 (C-6, major diastereoisomer), 36.55 (C-3, major diastereoisomer), 37.07 (C-3, minor diastereoisomer), 37.65 (C-5, major diastereoisomer), 37.70 (C-5, minor diastereoisomer), 38.30 (Me (mesyl), minor diastereoisomer), 38.41 (Me (mesyl), major diastereoisomer), 46.04 (C-1, major diastereoisomer), 47.18 (C-1, minor diastereoisomer), 48.40 (C-2, major diastereoisomer), 48.48 (C-2, minor diastereoisomer), 80.93 (C-4, minor diastereoisomer), 81.03 (C-4, major diastereoisomer); HRESIMS, *m/z* 231.066074 [M+Na$^+$] (Calcd. for $C_8H_{16}NaO_4S$, 231.066151).

4-Acetoxy-2-propyltetrahydrothiophene (**1**): Thioacetic acid (2.0 mL, 28 mmol) was added to a mixture of anhydrous potassium carbonate (5.5 g, 40 mmol), absolute acetonitrile (100 mL) and 18-crown-6 (0.26 g, 1 mmol). The mixture was stirred at room temperature for 15 min and 1,2-epoxy-4-heptyl mesylate **4** (4.2 g, 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 diethyl ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine successively and dried over $MgSO_4$. After concentration under vacuum, the residue was submitted to column chromatography (petroleum ether/ethyl acetate, 50:1) to give *cis*- and *trans*-isomer of **1** separately as a light yellow oil.

cis-Isomer (**1a**): Yield 1.6 g (43%). ^{1}H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.2 Hz, 3 H, H–C-3′), 1.32–1.48 (m, 2 H, H–C-2′), 1.58–1.74 (m, 2 H, H–C-1′), 1.80 (dt, *J* = 12.6, 7.8 Hz, 1 H, H–C-3), 2.08 (s, 3 H, Me(Ac)), 2.41 (dt, *J* = 12.6, 6.0 Hz, 1 H, H′–C-3), 2.89 (dd, *J* = 11.4, 6.6 Hz, 1 H, H–C-5), 3.16 (dd, *J* = 11.4, 6.6 Hz, 1 H, H′–C-5), 3.39 (m, 1 H, H–C-2), 5.31 (m, 1 H, H–C-4); ^{13}C NMR ($CDCl_3$) δ 13.86 (C-3′), 21.15 (Me(Ac)), 21.90 (C-2′), 35.35 (C-5), 40.07 (C-1′), 41.07 (C-3), 44.83 (C-2), 76.52 (C-4), 170.55 (C=O); HRESIMS, *m/z* 211.076359 [M+Na$^+$] (calcd for $C_9H_{16}NaO_2S$, 211.076321).

trans-Isomer (**1b**): Yield 1.7 g (45%). ^{1}H NMR ($CDCl_3$) δ 0.95 (t, *J* = 7.8 Hz, 3 H, H–C-3′), 1.42 (m, 2 H, H–C-2′), 1.59 (m, 1 H, H–C-1′), 1.65-1.75 (m, 2 H, H–C-3 and H′–C-1′), 2.08 (s, 3 H, Me(Ac)), 2.30 (dd, *J* = 13.2, 5.4 Hz, 1 H, H′–C-3), 2.93 (d, *J* = 12.0 Hz, 1 H, H–C-5), 3.23 (dd, *J* = 12.0, 4.8 Hz, 1 H, H′–C-5), 3.57 (m, 1 H, H–C-2), 5.50 (m, 1 H, H–C-4); ^{13}C NMR ($CDCl_3$) δ 13.99 (C-3′), 21.25 (Me(Ac)),

22.49 (C-2′), 37.07 (C-5), 38.81 (C-1′), 42.55 (C-3), 46.77 (C-2), 77.18 (C-4), 170.54 (C=O); HRESIMS, *m/z* 211.076385 [M+Na$^+$] (calcd for $C_9H_{16}NaO_2S$, 211.076321).

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