Preparation and odour of *cis*- and *trans*-2-methyltetrahydrofuran-3-thiol acetates

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The preparation of *cis*- and *trans*-2-methyltetrahydrofuran-3-thiol acetates from (*E*)-3-penten-1-ol is reported. The mesylate of (*E*)-3-penten-1-ol was converted into *trans*- or *cis*-2-methyl-3-hydroxytetrahydrofuran by oxidation with H_2O_2 and HCOOH or with $KMnO_4$. *cis*- or *trans*-2-Methyltetrahydrofuran-3-thiol acetate was prepared by mesylation and an S_N2 nucleophilic substitution with AcSH from *trans*- or *cis*-2-methyl-3-hydroxytetrahydrofuran respectively. The configuration of the products was confirmed by their synthesis. Olfactory evaluation of *cis*- and *trans*-2-methyltetrahydrofuran-3-thiol acetates indicated some differences both in odour feature and intensity.

Keywords: 2-methyltetrahydrofuran-3-thiol acetate, diastereoisomer, preparation, odour

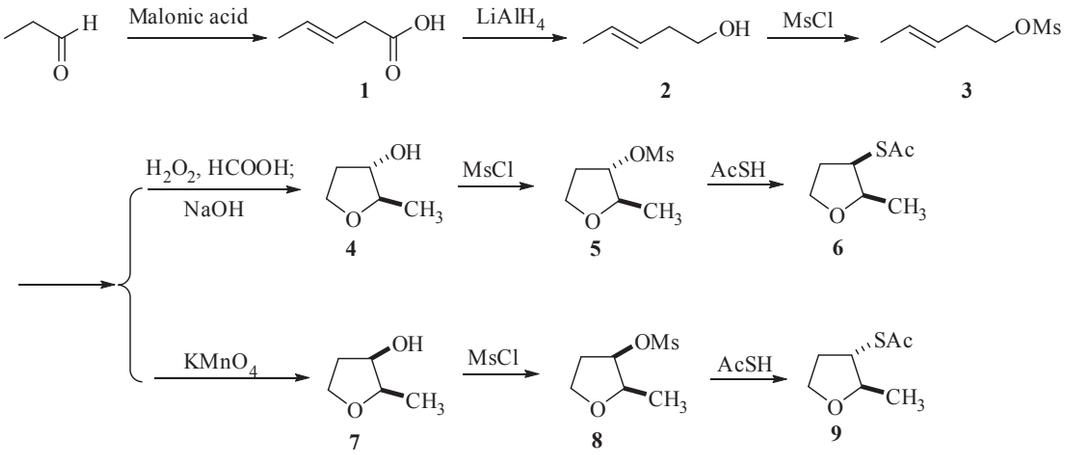
(±)-2-Methyltetrahydrofuran-3-thiol acetate has a sulfurous, roasted meat odour and has been approved as a flavour compound in 2011 with FEMA (Flavour and Extract Manufacturers' Association) No. 4686 shown on the FEMA GRAS (Generally Recognized as Safe) list 25.[1] This was 20 years later than the parent alcohol, (±)-2-methyltetrahydrofuran-3-thiol which was FEMA No. 3787 on the GRAS list 16.[2] It is well known for 2-methyltetrahydrofuran-3-thiol that the *trans*-isomer possesses a stronger meaty and roasted note while the *cis*-isomer is weaker and has a more sulfurous and musty note.[3] However, the *cis*/*trans*-mixture combines both notes in a full-body meat flavour. The odour discrepancy between the *trans*- and *cis*-isomers of aroma chemicals occurs commonly, such as methyl dihydroisojasmonate and methyl jasmonate, the *cis*-isomer of which is more desirable.[4–7] As far as we know, the odour properties of *trans*- and *cis*-isomers of 2-methyltetrahydrofuran-3-thiol acetate are still unknown.

The diastereoisomers of 2-methyltetrahydrofuran-3-thiol were prepared by an iodocyclisation approach starting from (*Z*)- and (*E*)-3-pentenols respectively, produced from 3-pentyn-1-ol reduced by catalytic hydrogenation or $LiAlH_4$.[3] The commercial form of 2-methyltetrahydrofuran-3-thiol is a mixture where the isomer ratio is about 1/1. This is blended by two products with different isomer ratios produced from different routes. We have developed a new approach to producing the *trans*- and *cis*-isomers of 2-methyltetrahydrofuran-3-thiol acetate in order to explore the odour properties of these isomers (Scheme 1).

Results and discussion

In our route, *trans*- and *cis*-isomers of 2-methyltetrahydrofuran-3-thiol acetate were obtained from the same intermediate, (*E*)-3-penten-1-ol **2**, which was prepared by the Knoevenagel condensation of propanal and malonic acid, followed by reduction with $LiAlH_4$. The Knoevenagel condensation gave a 10 : 1 mixture of (*E*)-3-pentenoic acid **1** and by-product (*E*)-2-pentenoic acid in about 30% yield. The mixture was used in the next step without further purification. (*E*)-3-Penten-1-ol **2** was converted into *trans*-2-methyl-3-hydroxytetrahydrofuran **4** by epoxidation of its mesylate with H_2O_2 and HCOOH followed by ring closure in the presence of NaOH in about 78% overall yield. The direct epoxidation of **2** without mesylation was also tried, which gave **4** in a relatively low yield of 59% (Scheme 2).

The transformation of *trans*-2-methyl-3-hydroxytetrahydrofuran **4** into *cis*-2-methyltetrahydrofuran-3-thiol acetate **6** was attempted by two different routes. In one route, **4** was reacted with MsCl to give *trans*-2-methyl-3-mesyloxytetrahydrofuran **5** in about 89% yield. This was converted into **6** in about 81% yield through an S_N2 nucleophilic substitution by AcSH. The alternative was that **4** underwent the Mitsunobu reaction with DIAD, Ph_3P and AcSH to produce **6** directly in about 65% yield (Scheme 3). The ^1H NMR spectra of the products obtained from these two ways identical to each other. To confirm the configuration of the synthesised 2-methyltetrahydrofuran-3-thiol acetate, *cis*-2-methyltetrahydrofuran-3-thiol acetate was prepared in about



Scheme 1 Preparation of *trans*- and *cis*-2-methyltetrahydrofuran-3-thiol acetates.

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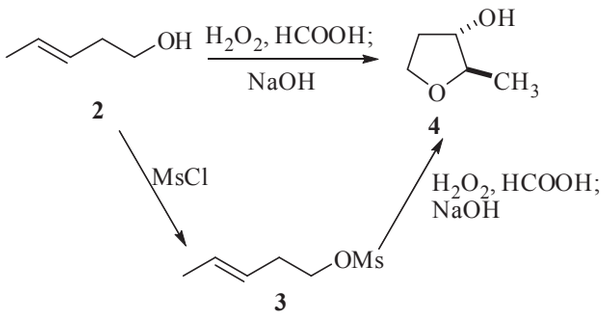
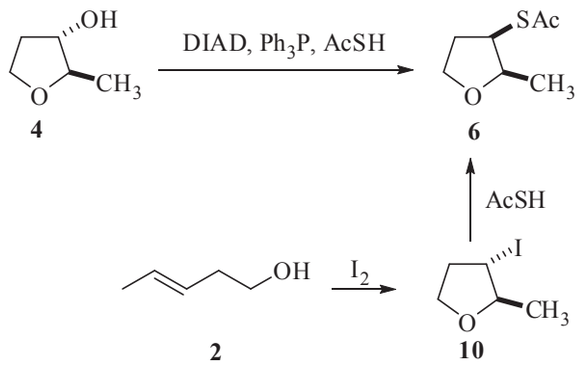


Scheme 2 Preparation of *trans*-2-methyl-3-hydroxytetrahydrofuran.



Scheme 3 Preparation of *cis*-2-methyltetrahydrofuran-3-thiol acetate by Mitsunobu reaction or iodocyclisation.

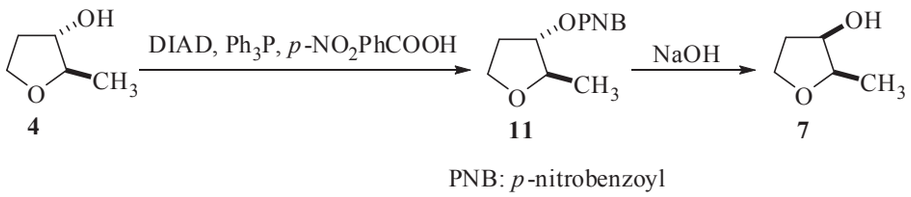
32% overall yield through an iodocyclisation of **2** followed by an S_N2 nucleophilic substitution with AcSH according to the literature method (Scheme 3).[3] As expected, product **6** obtained by epoxidation of **2** with H_2O_2 and HCOOH, followed by mesylation and nucleophilic substitution or by Mitsunobu reaction, has the same configuration as the iodocyclisation approach of **2** in the literature.

(*E*)-3-Penten-1-yl mesylate **3** was oxidised by $KMnO_4$ to give *cis*-2-methyl-3-hydroxytetrahydrofuran **7** in about 83% yield. An alternative approach was used to prepare **7**, in which *trans*-2-methyl-3-hydroxytetrahydrofuran **4** was converted into its *cis*-isomer **7** by the Mitsunobu reaction with DIAD, Ph_3P and *p*-NO_2PhCOOH followed by hydrolysis in about 62% overall yield (Scheme 4). The NMR spectra of the products from the two different routes were identical and showed significant differences from the data of its isomer **4**. *trans*-2-Methyltetrahydrofuran-3-thiol acetate **9** was obtained from **7** through a mesylation and an S_N2 nucleophilic substitution with AcSH.

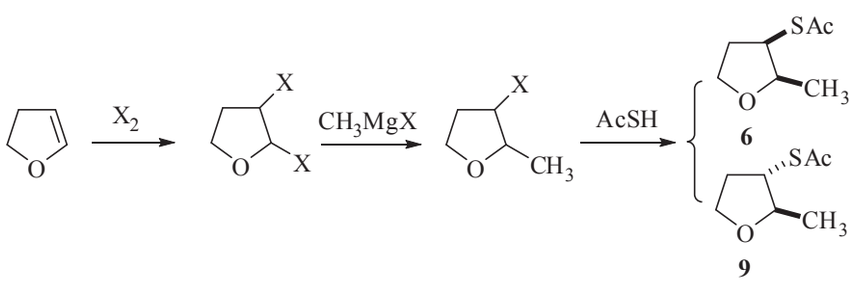
As far as we know, 2-methyltetrahydrofuran-3-thiol acetate is the precursor of 2-methyltetrahydrofuran-3-thiol in the industrial production. The mixture of *cis*- and *trans*-2-methyltetrahydrofuran-3-thiol acetate was obtained starting from 2,3-dihydrofuran by electrophilic addition of halogen, methylation with Grignard reagent and nucleophilic substitution by AcSH. Generally, bromine gave the *trans*-isomer as the major product (70%) whereas chlorine gave the *cis*-isomer as the major product (70%) (Scheme 5).

The odour of *trans*- and *cis*-isomers of 2-methyltetrahydrofuran-3-thiol acetate were evaluated. The *cis*-isomer presents a meaty aroma with a Chinese broccoli note; whereas the *trans*-isomer has a meaty aroma with pickled potherb mustard note. The *cis*-isomer has a stronger aroma than the *trans*-isomer. It is well known that odour differences between the two enantiomers also commonly exist. Thus only (+)-(1*R*,2*S*)-*cis*-methyl dihydroisojasmonate is sensorially active[8] after the (±)-*cis*-isomer was identified to be the only intense and characteristic component of the synthetic *trans*- and *cis*-mixture.[9] Therefore, the preparation of the four stereoisomers of 2-methyltetrahydrofuran-3-thiol acetate is under investigation in our laboratory in order to identify the odour properties of each stereoisomer.

In summary, both *trans*- and *cis*-2-methyltetrahydrofuran-3-thiol acetates have been prepared from (*E*)-3-penten-1-ol, which was easily accessible by the reduction of (*E*)-3-pentenoic acid obtained from the Knoevenagel condensation of propanal and malonic acid. The *trans*- and *cis*-isomers present some differences in odour feature and intensity. The route is suitable for the industrial production of *trans*- and *cis*-2-methyltetrahydrofuran-3-thiol acetates separately.



Scheme 4 The preparation of *cis*-2-methyl-3-hydroxytetrahydrofuran from *trans*-isomer by Mitsunobu reaction.



Scheme 5 The industrial production of 2-methyltetrahydrofuran-3-thiol acetate.

Experimental

Di-*iso*-propylazodicarboxylate (DIAD) and $LiAlH_4$ were purchased from Beijing Bailingwei Science and Technology Company, and the others were purchased from Beijing Huaxue Shiji Company. The NMR spectra were obtained on a Bruker AV300 MHz NMR (Bruker, Fällanden, Zürich, Switzerland). The high resolution mass spectra were performed on a Bruker Apex IV FTMS.

(*E*)-*3-Pentenoic acid* **(1):** Propanal (18 mL, 0.25 mol) was slowly added at 40 °C over 1 h to a mixture of malonic acid (78 g, 0.75 mol), piperidine (0.25 mL, 2.5 mmol) and xylene (100 mL). The reaction apparatus was equipped with a Dean–Stark trap for the continuous removal of water during the reaction. The reaction temperature was raised to reflux after the addition. When no more water was separated, the reaction mixture was cooled to room temperature and filtered to remove the excess malonic acid. Xylene was removed under reduced pressure. The residue was distilled under vacuum (0.4 kPa, 60–65 °C) [lit.[10] b.p. 66 °C (4 mmHg)] to give (*E*)-3-pentenoic acid **1** as a colourless oil (7.5 g, 30% yield). ^{1}H NMR ($CDCl_3$) δ 1.68 (3H, d, J = 6.0 Hz, Me(5)), 3.05 (2H, d, J = 5.7 Hz, H–C(2)), 5.54 (2H, m, H–C(3) and C(4)), 10–12 (1H, br, –COOH). ^{13}C NMR ($CDCl_3$) δ 17.9 (Me), 37.8(C(2)), 121.9 (C(4)), 130.0 (C(3)), 179.0 (C(1)). ^{1}H NMR data were identical to those reported in the literature.[10]

(E)-3-Penten-1-ol **(2):** Lithium aluminium hydride (3.8 g, 0.1 mol) was suspended in dry tetrahydrofuran (50 mL) under nitrogen. (*E*)-3-Pentenoic acid **1** (10 g, 0.1 mol) dissolved in dry tetrahydrofuran (30 mL) was added dropwise at 0–5 °C. After the addition, the reaction mixture was heated at reflux for 2 h. Then it was cooled to 0 °C and quenched by careful addition of distilled water (15 mL) and 10% sodium hydroxide solution (10 mL). The mixture was filtered over Na_2SO_4, and the filtrate was evaporated under reduced pressure (0.4 kPa, 35–40 °C) [lit.[11] b.p. 130–138 °C] to give (*E*)-3-pentenol **2** as a yellow oil (7.6 g, 88% yield). ^{1}H NMR ($CDCl_3$) δ 1.65 (3H, d, J = 6.3 Hz, Me(5)), 2.22 (2H, m, H–C(2)), 3.59 (2H, t, J = 6.3 Hz, H–C(1)), 5.38 (1H, m, H–C(4)), 5.57 (1H, m, H–C(3)). ^{13}C NMR ($CDCl_3$) δ18.0 (Me), 35.9 (C(2)), 62.0 (C(1)), 127.2 (C(4)), 128.1 (C(3)). The ^{1}H NMR data were identical with those reported in the literature.[11]

(E)-3-penten-1-yl mesylate **(3):** (*E*)-3-pentenol **2** (5 g, 58 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and cooled to 0 °C. Triethylamine (16.2 mL, 116 mmol) and methanesulfonylchloride (5.8 mL, 75.4 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% solution of HCl (30 mL) at 0–5 °C. The reaction mixture was then extracted three times with CH_2Cl_2, and the combined organic phases were washed once with saturated aqueous $NaHCO_3$ solution and once with saturated brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was distilled under vacuum (0.4 kPa, 100–105 °C) to give **3** as a yellow oil (8.7 g, 92% yield). ^{1}H NMR ($CDCl_3$) δ 1.64 (3H, d, J = 6.3 Hz, Me(C(5))), 2.39 (2H, q, J = 6.9 Hz, H–C(2)), 2.96 (3H, s, Me(mesyl)), 4.17 (2H, t, J = 6.9 Hz, H–C(1)), 5.36 (1H, m, H–C(4)), 5.57 (1H, m, H–C(3)). ^{13}C NMR ($CDCl_3$) δ 17.5 (Me(C(5)), 31.9 (C(2)), 36.8 (Me(mesyl)), 69.4 (C(1)), 124.5 (C(4)), 128.7 (C(3)). The ^{1}H NMR data corresponded with those reported in the literature.[11]

trans-*2-Methyl-3-hydroxytetrahydrofuran* **(4):** From (*E*)-3-penten-1-yl mesylate; compound **3** (7.5 g, 0.046 mol) was added to a mixture of 30% hydrogen peroxide (23 mL, 0.23 mol) and 88% formic acid (31 mL, 0.7 mol) over 1 h. The reaction mixture was kept at 40–45 °C during the addition. Then the mixture was stirred for 5 h at 40 °C. The mixture was cooled with ice bath and neutralised with cold 35% aqueous NaOH solution until pH 9 and then kept stirring for 3 h. The aqueous layer was extracted with ether and the organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was distilled under reduced pressure (0.1 kPa, 36–38 °C) to give **4** as a light yellow oil (4.0 g, 85% yield). ^{1}H NMR ($CDCl_3$) δ 1.16 (3H, d, J = 6.3 Hz, Me), 1.84 (1H, m, H–C(4)), 2.16 (1H, m, H–C(4)), 2.23 (1H, br, –OH), 3.82 (1H, m, H–C(3)), 3.87–4.01 (3H, m, H–C(2) and C(5)). ^{13}C NMR ($CDCl_3$) δ 18.8 (Me), 34.3 (C(4)), 66.0 (C(5)), 76.7 (C(3)), 81.7 (C(2)). The NMR data corresponded with those reported in the literature.[12]

From (*E*)-3-penten-1-ol **2**; compound **2** (1.7 g, 0.02 mol) was added to a mixture of 30% hydrogen peroxide (10 mL, 0.1 mol) and 88% formic acid (13 mL, 0.3 mol) during a period of 1 h. The reaction mixture was cooled and kept at 40–45 °C during the addition. After the addition, the mixture was stirred for 5 h at 40 °C. The mixture was cooled with an ice bath and neutralised with cold 35% sodium hydroxide aqueous solution until pH 9. The mixture was stirred at room temperature for 3 h. The aqueous layer was extracted with ether and the organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated under vacuum and the residue was purified by column chromatography (petroleum ether/ethyl acetate, 6 : 1) to give **4** as a light yellow oil (1.2 g, 59% yield). The NMR spectra of the product corresponded with those of the product obtained from **3**.

trans-*2-Methyl-3-mesyloxytetrahydrofuran* **(5):** *trans*-2-Methyl-3-hydroxytetrahydrofuran **4** (3.2 g, 31 mmol) was dissolved in dry dichloromethane (40 mL) and cooled to 0 °C. Triethylamine (9 mL, 62 mmol) and methanesulfonylchloride (3.0 mL, 40 mmol) were added in succession at 0–5 °C. The reaction mixture was stirred at room temperature overnight. The reaction mixture was treated with 10% HCl solution (30 mL) at 0–5 °C. The reaction mixture was then extracted three times with dichloromethane, and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine successively and dried over $MgSO_4$. After concentration under reduced pressure, the residue was distilled under vacuum (0.3 kPa, 80–85 °C) to give **5** as a light yellow oil (5.0 g, 89% yield). ^{1}H NMR ($CDCl_3$) δ 1.26 (3H, d, J = 6.6 Hz, Me–C(2)), 2.18 (1H, m, H–C(3)), 2.24 (1H, m, H–C(3)), 3.04 (3H, s, Me(mesyl)), 3.89 (1H, td, J = 9.3, 6.6 Hz, H–C(5)), 4.01 (1H, td, J = 8.4, 3.3 Hz, H–C(5)), 4.12 (1H, m, H–C(2)), 4.82 (1H, m, H–C(3)). ^{13}C NMR δ 18.5 (Me–C(2)), 32.5 (C(4)), 38.4 (Me(mesyl)), 66.3 (C(5)), 79.7 (C(2)), 85.1 (C(3)). HRESIMS, *m/z* 203.03502 [M + Na$^+$] (calcd for $C_6H_{12}NaO_4S$, 203.03485).

cis-*2-Methyltetrahydrofuran-3-thiol acetate* **(6):** From *trans*-2-methyl-3-mesyloxytetrahydrofuran (**5);** thioacetic acid (0.9 g, 12 mmol) was added to a mixture of anhydrous potassium carbonate (2.2 g, 16 mmol), absolute acetonitrile (50 mL) and 18-crown-6 (0.1 g, 0.4 mmol). The mixture was stirred at room temperature for 20 min and *trans*-2-methyl-3-mesyloxytetrahydrofuran **5** (1.4 g, 8 mmol) was added dropwise. After the addition, the mixture was heated at reflux for 24 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 in succession and dried over $MgSO_4$. After concentration under vacuum, the residue was submitted to column chromatography (petroleum ether/ethyl acetate, 10 : 1) to give **6** as a light yellow oil (1.04 g, 81% yield). ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, d, J = 6.3 Hz, Me), 1.93 (1H, m, H–C(4)), 2.48 (1H, m, H–C(4)), 2.34 (3H, s, Me(Ac)), 3.75 (1H, td, J = 8.4, 6.3 Hz, H–C(5)), 3.90 (1H, td, J = 8.4, 6.3 Hz, H–C(5)), 4.13 (1H, m, H–C(2)), 4.05 (1H, m, H–C(3)). ^{13}C NMR ($CDCl_3$) δ 16.8 (Me), 30.6 (Me(Ac)), 33.5 (C(4)), 46.3 (C(3)), 65.9 (C(5)), 76.5 (C(2)), 195.4 (C=O). HRESIMS, *m/z* 161.06313 [M + H$^+$] (calcd for $C_7H_{13}O_2S$, 161.06308).

From *trans*-2-methyl-3-hydroxytetrahydrofuran **4** by the Mitsunobu reaction;[13] a solution of *trans*-2-methyl-3-hydroxytetrahydrofuran **4** (1.6 g, 15.6 mmol) in tetrahydrofuran (40 mL) was treated with Ph_3P (8.4 g, 32 mmol), DIAD (6.5 g, 32 mmol) and thioacetic acid (2.43 g, 32 mmol). After the addition, the mixture was stirred for 1 day at room temperature. The solvent was removed under reduced pressure. The residue was purified twice by flash column chromatography (petroleum ether/ethyl acetate, 10 : 1) to give **6** as a yellow oil (1.6 g, 65% yield). The NMR spectra of the product were identical with those of the product obtained from **5**.

From (*E*)-3-penten-1-ol **2** by iodocyclisation; **2** (2.6 g, 0.03 mol) was added to a mixture of iodine (11.4 g, 0.045 mol) and methanol (40 mL) dropwise. The mixture was stirred at room temperature for 2 h. Then $NaHCO_3$ (5 g, 0.06 mol) was added in batches and the reaction mixture was stirred for 5 h at room temperature. Saturated aqueous sodium thiosulfate solution was added dropwise until the reddish-brown colour disappeared. The reaction mixture was filtered, and the filtrate

was extracted four times with CH_2Cl_2. The combined organic phases were washed once with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude product *trans*-2-methyl-3-iodotetrahydrofuran **10** as a brown oil (2.5 g, 40% yield). ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, d, J = 6.0 Hz, Me), 2.28 (1H, m, H–C(4)), 2.56 (1H, m, H–C(4)), 3.65 (1H, m, H–C(3)), 3.88 (2H, m, H–C(5)), 4.07 (1H, m, H–C(2)). ^{13}C NMR ($CDCl_3$) δ 17.6 (Me), 24.9 (C(3)), 38.2 (C(4)), 66.8 (C(5)), 84.0 (C(2)). HRESIMS, *m/z* 212.97770 [M+H$^+$] (calcd for $C_5H_{10}IO$, 212.97708).

Thioacetic acid (1.1 g, 15 mmol) was added to a mixture of anhydrous potassium carbonate (2.8 g, 20 mmol), absolute acetonitrile (60 mL) and 18-crown-6 (0.13 g, 0.5 mmol). The mixture was stirred at room temperature for 20 min and **10** (2.1 g, 10 mmol) was added. After the addition, the mixture was heated at reflux overnight. The reaction mixture was cooled to room temperature and filtered. The filtrate was acidified by addition of 5% aqueous HCl, and extracted four times with diethyl ether. The combined organic phases were washed once with saturated aqueous $NaHCO_3$ solution and once with saturated brine, dried over magnesium sulfate, and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 10 : 1) to give **6** as a light yellow oil (0.32 g, 80% yield). The NMR spectra of the product were identical with those of the product obtained above.

cis-*2-Methyl-3-hydroxytetrahydrofuran* **(7):** From (*E*)-3-penten-1-yl mesylate **3;**[14] a solution of $KMnO_4$ (4 g, 25 mmol) in acetone/water (70 mL, 2.5 : 1) was added at 0 °C over 20 min to a solution of **3** (3.3 g, 20 mmol) in acetone (50 mL). The temperature of the reaction mixture were kept at 0 °C stirring for 3 h. A solution of $NaHSO_3$ (45 mL, 40% in water) was added. The mixture was filtered through a pad of Celite and the acetone was removed *in vacuo*. The residue was saturated by addition of NaCl and extracted with CH_2Cl_2. After drying and evaporation of solvents *in vacuo* the remaining crude was purified by column chromatography (petroleum ether/ethyl acetate, 6 : 1) to give **7** as a light yellow oil (1.7 g, 83% yield). ^{1}H NMR ($CDCl_3$) δ 1.27 (3H, d, J = 6.3 Hz, Me), 1.93 (1H, m, H–C(4)), 2.22 (1H, m, H–C(4)), 3.73 (2H, m, H–C(3) and C(5)), 4.03 (1H, dd, J = 15.9, 8.1 Hz, H–C(5)), 4.17 (1H, m, H–C(2)). ^{13}C NMR ($CDCl_3$) δ 13.7 (Me), 35.4 (C(4)), 65.5 (C(5)), 72.8 (C(3)), 78.6 (C(2)). The NMR data were matched with those reported in the literatiure.[12].

From *trans*-2-methyl-3-hydroxy-tetrahydrofuran **4** by Mitsunobu reaction; *trans*-2-methyl-3-hydroxy-tetrahydrofuran **4** (3.1 g, 30 mmol) was dissolved in tetrahydrofuran (80 mL). Triphenylphosphine (16.8 g, 64 mmol) and *p*-nitrobenzoic acid (10.7 g, 64 mmol) were added with stirring. DIAD (13 g, 64 mmol) was added dropwise. After the addition, the mixture was stirred for 1 day at room temperature. The solution was concentrated under reduced pressure to give a viscous orange oil that was dissolved in a minimal amount of CH_2Cl_2 and purified twice by flash chromatography (ether/ethyl acetate, 8 : 1) to give *cis*-2-methyl-3-*p*-nitrobenzoyloxytetrahydrofuran **11** as a white crystalline solid (m.p. 171–173 °C) (5.2 g, 69% yield). ^{1}H NMR ($CDCl_3$) δ 1.30 (3H, d, J = 6.3 Hz, Me), 2.12 (1H, m, H–C(4)), 2.46 (1H, m, H–C(4)), 3.83 (1H, m, H–C(5)), 4.04 (1H, m, H–C(5)), 4.12 (1H, m, H–C(2)), 5.53 (1H, m, H–C(3)), 8.21 (2H, d, J = 9 Hz, H-aryl), 8.29 (2H, d, J = 9 Hz, H-aryl). ^{13}C NMR ($CDCl_3$) δ 14.3 (Me), 33.6 (C(4)), 66.0 (C(5)), 77.2 (C(3)), 77.5 (C(2)), 123.6 (C(3′) and C(5′) (aryl)), 130.7 (C(2′) and C(6′) (aryl)), 135.4 (C(1′) (aryl)), 150.6 (C(4′) (aryl)), 164.2 (C=O). HRESIMS, *m/z* 252.08728 [M+H$^+$] (calcd for $C_{12}H_{13}NO_5$, 252.08665). To a mixture of NaOH (3.2 g, 80 mmol), methanol/tetrahydrofuran (62 mL, 30 : 1) was added **11** (6 g, 24 mmol) at room temperature. The mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated *in vacuo*. Distilled water was added to the residue, and the mixture was extracted four times with diethyl ether. The combined organic phases were washed once with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (petroleum ether/ethyl acetate, 6 : 1) to give **7** as a light yellow oil (2.2 g, 90% yield). The NMR data were consistent with those of the product obtained above.

cis-*2-Methyl-3-mesyloxytetrahydrofuran* **(8):** *cis*-2-Methyl-3-hydroxytetrahydrofuran **7** was converted to its mesylate **8** by the same procedure as shown for **5**. 90% yield. ^{1}H NMR ($CDCl_3$) δ 1.33 (3H, d, J = 6.6 Hz, Me–C(2)), 2.34 (2H, m, H–C(4)), 3.05 (3H, s, Me(mesyl)), 3.80 (1H, td, J = 8.4, 5.4 Hz, H–C(5)), 4.08 (1H, q, J = 8.1 Hz, H–C(5)), 3.95 (1H, qd, J = 6.3, 3.6 Hz, H–C(2)), 5.13 (1H, ddd, J = 5.4, 3.6, 2.1 Hz, H–C(3)). ^{13}C NMR δ 14.4 (Me–C(2)), 34.0 (C(4)), 38.5 (Me(mesyl)), 65.8 (C(5)), 77.2 (C(2)), 81.9 (C(3)). HRESIMS, *m/z* 181.05317 [M+H$^+$] (calcd for $C_6H_{13}O_4S$, 181.05291).

trans-*2-methyltetrahydrofuran-3-thiol acetate* **(9):** *cis*-2-Methyl-3-mesyloxytetrahydrofuran **8** reacted with AcSH to give **9** according to the procedure similar to that for **6**. 85% yield. ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, d, J = 6.0 Hz, Me–C(2)), 1.85 (1H, m, H–C(4)), 2.49 (1H, m, H–C(4)), 2.34 (3H, s, Me(Ac)), 3.52 (1H, td, J = 8.7, 7.2 Hz, H–C(5)), 3.96 (1H, td, J = 8.7, 5.7 Hz, H–C(5)), 3.71–3.88 (2H, m, H–C(2) and C(3)). ^{13}C NMR δ 19.2 (Me), 30.6 (Me(Ac)), 33.2 (C(4)), 46.6 (C(3)), 66.7 (C(5)), 79.9 (C(2)), 195.3 (C=O). HRESIMS, *m/z* 161.06319 [M+H$^+$] (calcd for $C_7H_{13}O_2S$, 161.06308).

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