

cis-2-Pentenyl Moiety from 5,6-Dihydro-2*H*-thiopyran. A Convenient Synthesis of *cis*-Jasmone

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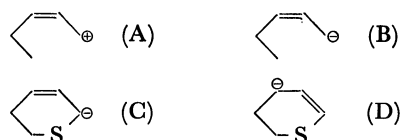
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Synopsis. A method for the synthesis of *cis*-jasmone from 5,6-dihydro-2*H*-thiopyran is described. Formation of *cis*-2-pentenyl moiety was achieved by reductive desulfurization of the 2*H*-thiopyran derivative obtained by the alkylation of 5,6-dihydro-2*H*-thiopyran with epichlorohydrin.

The construction of *cis*-2-pentenyl moiety has been the subject of jasmonoid syntheses.^{1a-c)} Preparation of the *cis*-pentenyl group by elaborated routes has been reported, *e.g.*, the partial hydrogenation of carbon-carbon triple bond,^{1d)} including the formation of 2-pentenyl group,^{1e)} the Wittig reaction of formylmethyl group with propylenetriphenylphosphorane under salt-free condition,^{1f)} and 1,5-sigmatropic rearrangement of 1-(1-propenyl)spiro[2.5]octan-4-one.^{1g)}

The dipole inversion (umpolung)²⁾ of *cis*-2-pentenyl cation (A) derived from *cis*-2-pentenyl halide would be *cis*-2-pentenide ion (B) which promises a novel approach for jasmonoid synthesis. A synthetic equivalent of the carbanion (B) is considered to be 5,6-dihydro-2*H*-thiopyran-2-ide ion (C). From our preliminary experiments, the regioselective alkylation of ambident carbanions (C) and (D) with epichlorohydrin has been found to occur exclusively at C-2 carbon atom.³⁾ This led us to investigate the novel synthesis of *cis*-jasmone.

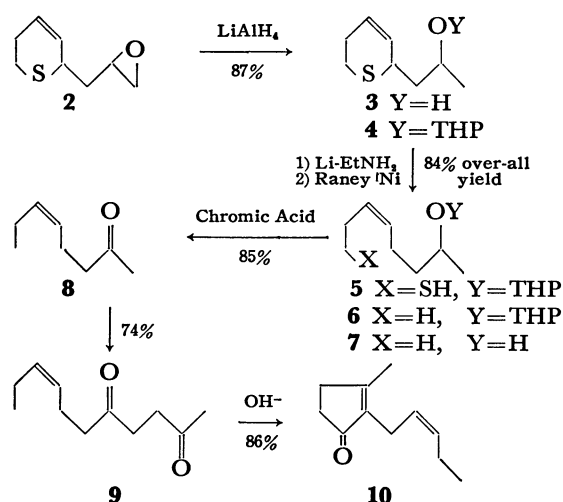


Treatment of 5,6-dihydro-2*H*-thiopyran (**1**)⁴⁾ with 1.1 equivalents of *s*-butyllithium in tetrahydrofuran (THF) at -78°C and subsequent addition of epichlorohydrin gave the 2-alkylated product **2** in 95% yield. Product **2** was contaminated with less than 2% of the corresponding 4-alkylated product. Reduction of **2** in THF at room temperature with lithium aluminum hydride afforded the alcohol **3**. Reductive desulfurization of the corresponding tetrahydropyranyl ether of **3** was performed by a two-step operation: treatment of **4** with lithium metal-ethylamine⁵⁾ at *ca.* -25°C and subsequent reduction of the thiol **5** with Raney nickel (W-2)⁶⁾ in methanol at $25-28^\circ\text{C}$, giving *cis*-7-tetrahydropyranyloxy-3-octene (**6**) in 84% over-all yield. Acetal exchange reaction of **6**⁷⁾ with *p*-toluenesulfonic acid-methanol and subsequent oxidation with chromic acid⁸⁾ gave *cis*-5-octen-2-one (**8**)⁹⁾ in 85% yield.

The conversion of the ketone **8** into *cis*-jasmone was achieved by Harper and Smith,¹⁰⁾ the preparation of dihydrojasmone from 2-octanone being established.¹⁾ The cross-coupling of enolate anions from 2-octanone and acetone has been found to be promoted by copper(II) chloride in *N,N*-dimethylformamide.¹¹⁾ According

to the method of Ito *et al.* **8** could react with acetone to give diketone **9** in 74% yield. Refluxing of **9** in aqueous 2% potassium hydroxide afforded *cis*-jasmone in 86% yield.¹²⁾

The *cis* double bonds of the products **8**, **9**, and **10** were analyzed by comparing their spectral data with those reported.^{9,11,12)} The results indicate that the *cis* double bonds of the intermediates **6** and **7** are retained during the course of conversion from **4** to **8**.



Experimental

Boiling points were indicated by air bath temperature without correction. NMR spectra were recorded on a Hitachi R-24 instrument. IR spectra were taken with JASCO model IRA-1 spectrometer. Analytical TLC was performed on commercial glass plates bearing 0.1–0.2 mm layer of Merck silica gel PF-254.

5,6-Dihydro-2*H*-thiopyran (1). An Improved Method: A mixture of 4-hydroxytetrahydrothiopyran¹³⁾ (1.30 g, 11 mmol) and a catalytic amount of KHSO_4 was heated to $250-300^\circ\text{C}$ under N_2 for 10 min and then distilled. After work-up in the usual manner, 0.90 g (82%) of **1** was obtained; bp $74-75^\circ\text{C}/60$ Torr (lit.⁴⁾ bp $35-36^\circ\text{C}/12$ Torr; IR (neat) 3020 ($\text{HC}=\text{CH}$), 1652 cm^{-1} ; NMR (CCl_4) δ 2.30 (m, 2H, $\text{CH}_2=\text{C}$), 2.65 (m, 2H, $\text{CH}_2=\text{S}$), 3.04 (m, 2H, $\text{S}-\text{CH}_2-\text{C}=\text{CH}$), 5.75 (m, 2H, $\text{HC}=\text{CH}$).

2-(2,3-Epoxypropyl)-5,6-dihydro-2*H*-thiopyran (2). *s*-BuLi in pentane (1.5 M, 2.5 ml, 3.8 mmol) was added dropwise to a solution of **1** (350 mg, 3.5 mmol) in THF (15 ml) with stirring under N_2 at -78°C for 1 h. To this mixture was added epichlorohydrin (336 mg, 3.6 mmol) with stirring at -78°C for 1 h and at room temp for an additional 1 h. The reaction was terminated by a few drops of water. The mixture was treated in the usual manner and the residue was subjected to short-path distillation to give **2** (520 mg, 95%); bp $84-86^\circ\text{C}/9$ Torr; IR (neat) 3024 ($\text{HC}=\text{CH}$), 1658 cm^{-1} ($\text{C}=\text{C}$); NMR (CCl_4) δ 3.38 (m, 1H, $\text{HC}=\text{S}$), 5.75 (m, 2H, $\text{HC}=\text{CH}$). Found:

C, 61.26; H, 7.82%. Calcd for $C_8H_{12}OS$: C, 61.50; H, 7.74%.

2-(2-Hydroxypropyl)-5,6-dihydro-2H-thiopyran (3). A THF solution (4 ml) of **2** (344 mg, 2.2 mmol) was added to a suspension of $LiAlH_4$ (100 mg, 2.6 mmol) in ether (12 ml) at 0 °C under N_2 . The mixture was stirred at 0 °C for 2 h and at room temp for 11 h and quenched with water at 0 °C until a white precipitate formed. The white solid was filtered off and the filtrate was concentrated. The residue was chromatographed over silica gel (2 g) with hexane-THF (10:1) to give **3** (340 mg, 87%): TLC R_f 0.30 (hexane-THF, 4:1); IR (neat) 3360 (OH), 3020 (HC=), 1654 cm^{-1} ; NMR ($CDCl_3$) δ 1.22 (d, $J=6.5$ Hz, 3H, CH_3), 1.55–1.94 (m, 2H), 2.29 (m, 2H, CH_2 -C=), 2.69 (m, 2H, CH_2 -S), 2.98 (s, 1H, OH), 3.41 (m, 1H, CH-S), 3.96 (m, 1H, CH-O), 5.75 (m, 2H, HC=CH). The analytical sample was prepared by short-path distillation at 50–55 °C/0.001 Torr. Found: C, 60.62; H, 9.07%. Calcd for $C_8H_{14}OS$: C, 60.72; H, 8.92%.

2-(2-Tetrahydropyranyloxypropyl)-5,6-dihydro-2H-thiopyran (4) was prepared from **3** (88 mg, 0.56 mmol) and dihydropyran (100 mg, 1.20 mmol) in benzene (2 ml) in the presence of *p*-toluenesulfonic acid (5 mg) in 89% yield: bp 67–72 °C/0.001 Torr; IR (neat) 3015 (HC=), 1652 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.20 (m, 3H, CH_3), 1.62 (m, 8H), 2.26 (m, 2H, CH_2 -C=), 2.67 (m, 2H, CH_2 -S), 3.17–4.20 (m, 4H, CH_2 -O, CH-O, CH-S), 4.69 (m, 1H, O-CH-O), 5.73 (m, 2H, HC=CH). Found: C, 64.19; H, 9.22%. Calcd for $C_{13}H_{22}O_2S$: C, 64.42; H, 9.15%.

cis-7-Tetrahydropyranyloxy-3-octene (6). Lithium metal (11 mg, 1.6 mmol) was added at –25 °C to a solution of **4** (30 mg, 0.12 mmol) in $EtNH_2$ (3 ml), stirring being continued for 1 h. The mixture was quenched with water. After evaporation of the solvent, the residue was extracted with $AcOEt$, washed with brine, and concentrated, then subjected to column chromatography of silica gel with hexane-THF (10:1) to give the thiol **5** (28 mg, 93%): TLC R_f 0.35 (hexane-THF, 10:1); IR (neat) 3000 (HC=), 1654 cm^{-1} (C=C); NMR ($CDCl_3$) δ 1.16 (m, 3H, CH_3), 1.27–2.70 (m, 15H), 3.15–4.10 (m, 3H), 4.67 (m, 1H, O-CH-O), 5.41 (m, 2H, HC=CH). Without further purification a $MeOH$ solution (2 ml) of **5** (28 mg, 0.11 mmol) was added to a suspension of Raney Ni (W-2) (60 mg) in $MeOH$ (1 ml) over a period of 5 min at room temp. The mixture was stirred for 1 h at 25–28 °C, diluted with acetone, filtered and concentrated. The residue was chromatographed on silica gel (2 g) with hexane-THF (50:1) to give **6** (22 mg, 90%): TLC R_f 0.62 (hexane-THF, 15:1); IR (neat) 3040 cm^{-1} (HC=); NMR ($CDCl_3$) δ 0.95 (t, $J=7.2$ Hz, 3H, CH_3), 1.15 (m, 3H, CH_3), 1.30–2.33 (m, 12H), 3.20–4.07 (m, 3H), 4.69 (m, 1H, O-CH-O), 5.37 (m, 2H, HC=CH). The analytical sample was obtained by short-path distillation at 71–75 °C/1.0 Torr. Found: C, 73.36; H, 11.62%. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39%.

cis-5-Octen-2-ol (7). To a $MeOH$ solution (3 ml) of **6** (50 mg, 0.24 mmol) was added *p*-toluenesulfonic acid (5 mg) at 0 °C. After being stirred for 5 min at 0 °C, then 1.5 h at room temp the mixture was worked up in the usual manner to give the alcohol **7** (30 mg, 99%); bp 62–65 °C/13 Torr; TLC R_f 0.30 (hexane-THF, 10:1); IR (neat) 3330 (OH), 3000 (HC=), 1652 cm^{-1} (C=C); NMR ($CDCl_3$) δ 0.96 (t, $J=7.2$ Hz, 3H, CH_3), 1.17 (d, $J=6.2$ Hz, 3H, CH_3), 1.20–2.35 (m, 7H), 3.76 (m, 1H, CH-O), 5.38 (m, 2H, HC=CH). Found: C, 75.05; H, 12.87%. Calcd for $C_8H_{16}O$: C, 74.97; H, 12.85%.

cis-5-Octen-2-one (8). To a solution of **7** (30 mg, 0.23 mmol) in ether (3 ml) was added aqueous chromic acid⁹ (1.3 M, 0.1 ml) at 0 °C. The mixture was stirred for 30 min at 0 °C and for 1 h at room temp. The organic phase was separated and worked up in the usual manner to give **8** (25 mg, 85%); bp 110–115 °C/760 Torr (lit.⁹) bp 54–57 °C/10 Torr, whose IR and NMR spectra were identical with those of the authentic compound.⁹

cis-8-Undecen-2,5-dione (9).¹¹ The compound **8** (30 mg, 0.24 mmol) was added dropwise to a solution of *i*- Pr_2N Li in THF (0.9 M, 1.3 ml, 1.2 mmol) at –78 °C under N_2 . Stirring was continued for 15 min and then acetone (41 mg, 0.47 mmol) was added over a period of 10 min. The mixture was stirred for 15 min at –78 °C and then a solution of copper(II) chloride (184 mg, 1.1 mmol) in DMF (1 ml) was added at –78 °C. The mixture was kept at –78 °C for 30 min, warmed to room temp, and stored for 30 min. The solution was poured into ice cooled aqueous 5% HCl (5 ml) and extracted with ether. The extract was worked up in the usual manner and the residue was subjected to preparative GLPC¹⁴ to give **9** (32 mg, 74%), whose spectral data were in agreement with those of the authentic sample.¹²

cis-Jasmone (10). A solution of diketone **9** (20 mg, 0.11 mmol) in aqueous 2% KOH was refluxed for 3 h. After work-up in the usual manner, 17 mg (86%) of **10** was obtained, bp 105–110 °C/3 Torr (lit.¹²) bp 93–97 °C/0.8 Torr, which was identified as *cis*-jasmone by comparison of the IR and NMR spectra of **10** with those reported.¹²

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- The condition of GLPC: R_f 18 min, 3 m $\times$ 4 mm column of 10% SE-30 on Chamelite CK 80–100 mesh at 140 °C with a flow rate of 20 ml/min.