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

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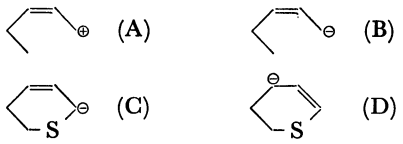
Synopsis. A method for the synthesis of *cis*-jasmone from 5,6-dihydro-2*H*-thiopyran is described. Formation of *cis*-2-pentenyl moiety was achieved by reductive desulfurization of the 2*H*-thiopyran derivative obtained by the alkylation of 5,6-dihydro-2*H*-thiopyran with epichlorohydrin.

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-pentynyl group,[1e] the Wittig reaction of formylmethyl group with propylidenetriphenylphosphorane under salt-free condition ,[1f] and 1,5-sigmatropic rearrangement of 1-(1-propenyl)spiro[2.5]octan-4-one.[1g]

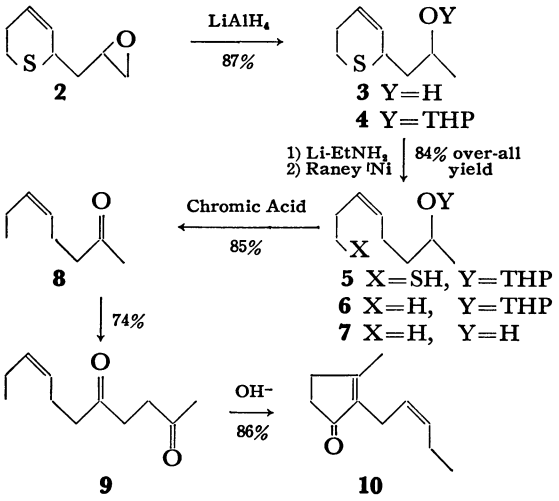
The dipole inversion (umpolung)[2] of *cis*-2-pentenyl cation (A) derived from *cis*-2-pentenyl halide would be *cis*-2-pentenide ion (B) which promises a novel approach for jasmonoid synthesis. A synthetic equivalent of the carbanion (B) is considered to be 5,6-dihydro-2*H*-thiopyran-2-ide ion (C). 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–ethylamine[5] at *ca.* −25 °C and subsequent reduction of the thiol **5** with Raney nickel (W-2)[6] in methanol at 25—28 °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 acid[8] 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-2H-thiopyran (1). *An Inproved Method*: A mixture of 4-hydroxytetrahydrothiopyran[13] (1.30 g, 11 mmol) and a catalytic amount of $KHSO_4$ was heated to 250—300 °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 °C/60 Torr (lit,[4] bp 35—36 °C/12 Torr); IR (neat) 3020 (HC=), 1652 cm^{-1}; NMR (CCl_4) δ 2.30 (m, 2H, CH_2–C=), 2.65 (m, 2H, CH_2–S), 3.04 (m, 2H, S–CH_2–C=), 5.75 (m, 2H, HC=CH).

2-(2,3-Epoxypropyl)-5,6-dihydro-2H-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 °C/9 Torr; IR (neat) 3024 (HC=), 1658 cm^{-1} (C=C); NMR (CCl_4) δ 3.38 (m, 1H, HC–S), 5.75 (m, 2H, HC=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 acid[8] (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_2NLi 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 GLPC[14] 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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14) The condition of GLPC: R_t 18 min, 3 m×4 mm column of 10% SE-30 on Chamelite CK 80—100 mesh at 140 °C with a flow rate of 20 ml/min.