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Synthesis of Deoxyobtusilactone A

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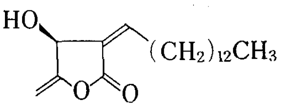
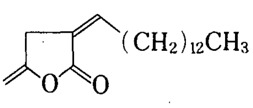
Deoxyobtusilactone A was synthesized from 1-tetradecene by a route involving [3,3]-sigmatropic rearrangement of 1,1-dichloro-2-(2-propenoxy)-1-hexadecene, followed by Favorskii rearrangement of the resulting γ,δ-unsaturated α,α-dichloroketone.

Keywords——α,α-dichloroketone; [3,3]sigmatropic rearrangement; Favorskii rearrangement; obtusilactone A; deoxyobtusilactone A

In an earlier paper[1] we reported a general route to γ,δ-unsaturated α,α-dichloroketones from allyl 2,2,2-trichloroethyl ethers *via* the [3, 3]sigmatropic rearrangement of intermediary 2,2-dichlorovinyl ethers. γ,δ-Unsaturated α,α-dichloroketones are of particular interest, since they can serve as effective synthetic precursors possessing three functional groups. We have exploited some of their reactions with reagents such as methoxide and hydroxide and applied the latter reaction for a new efficient synthesis of the deoxy analog (**14**) of naturally occurring obtusilactone A.



obtusilactone A



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The reactions of phenyl and alkyl 1,1-dichloro-3-butenyl ketones[1] with methoxide proceeded in different ways. Treatment of 2,2-dichloro-1-phenyl-4-penten-1-one (**1**) with 2.1 mol equivalents of sodium methoxide gave 1,1,4-trimethoxy-1-phenyl-2-pentanone (**2**) as a reasult of methoxide addition. The product is similar to that formed from 2,2-dichloroketones, as reported previously.[2] 4,4-Dichloro-2-methyl-6-hepten-3-one (**3**) reacted with sodium methoxide and hydroxide to give 2-isopropylidene-4-pentenoic acid methyl ester (**4**) and 2-isopropylidene-4-pentenoic acid (**5**), respectively, the formation of which could be explained in terms of Favorskii rearrangement.

In view of the formation of the α-allyl-α,β-unsaturated acid by the above reaction with sodium hydroxide, we were tempted to apply this reaction to a synthesis of the deoxy analog (**14**) of obtusilactone A. Obtusilactones are a series of natural products isolated from the

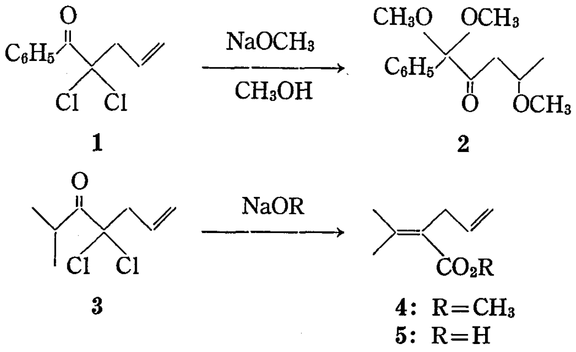

Chart 1

plant *Lindera obtusiloba* Blume, and some of them were reported to possess cytotoxic activity.3) However, synthetic approaches to obtusilactones have been reported in only a few papers.4)

Synthesis of deoxyobtusilactone A (**14**) has been achieved as outlined in Chart 2. 4,4-Dichloro-1-nonadecen-5-one (**11**) was obtained from 1,1,1-trichloro-2-(2-propenoxy)hexadecane (**9**) by dehydrochlorination, followed by [3, 3]sigmatropic rearrangement. 1,1,1-Trichloro-2-hexadecanol (**8**) was obtained by hydrogenation of 1,1,1-trichloro-4-hexadecen-2-ol (**7**) which was prepared by the reaction of 1-tetradecene (**6**) with chloral in the presence of anhydrous ferric chloride according to the previously reported method.5) Then **8** was converted into the allyl ether **9** by reaction with allyl bromide in the phase transfer system. The reaction of **11** with sodium hydroxide in water–dioxane under reflux gave the desired product, 2-(2-propenyl)-2-hexadecenoic acid (**12**), as a mixture of *E* and *Z* forms. The crude mixture, **12**, was iodolactonized by a method similar to that reported previously.6) The geometric isomer mixture of α-alkylideneiodolactones **13a**, **b** obtained was separated by column chromatography on silica gel using hexane–benzene as an eluent. The less polar isomer **13a** obtained from **11** in 31% overall yield was assigned as the *Z* isomer on the basis of the higher field resonance at 6.14—6.33 ppm for vinyl proton in the proton magnetic resonance (PMR) spectrum. The other isomer **13b** obtained from **11** in 24% overall yield was assigned as the *E* isomer on the basis of the lower field resonance at 6.64—6.87 ppm. Attempt to obtain deoxyobutsilactone A (**14**) by dehydroiodination under various conditions encountered difficulty, presumably owing to easy isomerization of **14** by base-catalyzed prototropy under the reaction conditions used. A method using excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in isopropyl ether at −20—0°C gave deoxyobtusilactone A (**14**) in 7% yield. The method previously reported6) for the dehydro-

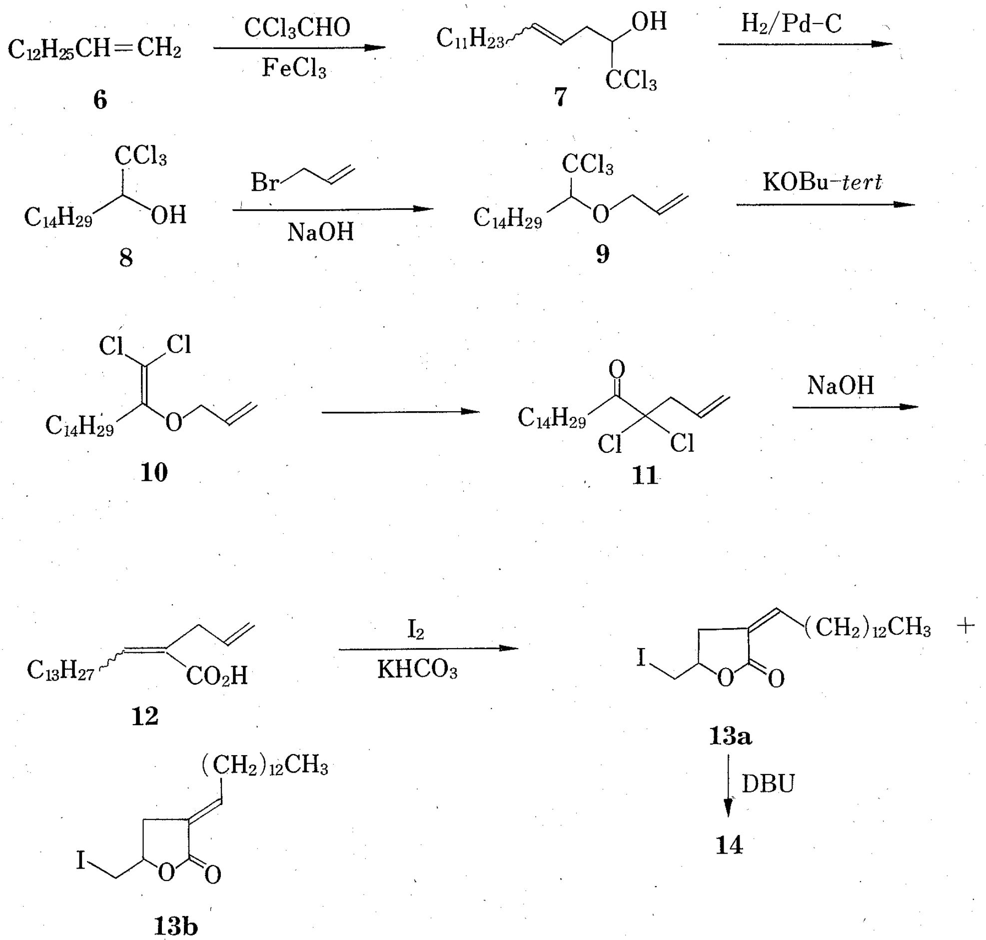

Chart 2

iodination of γ-iodomethyl-γ-butyrolactones using DBU in benzene at 60—80°C failed,' yielding only a tarry material. The structiure of **14** was confirmed on the bass of the PMR and carbon magnetic resonance (CMR) spectra, in which the signals were closely related to the coresponding signals deoxyobtusilactone$^{4a)}$ and obtusilactone A$^{3a)}$ reported previously.

Experimental

1,1,4-Trimethoxy-1-phenyl-2-pentanone (2)——A solution of 2,2-dichloro-1-phenyl-4-penten-1-one (1) (6.9 g, 0.03 mol) in methanol (10 ml) was added to a 1 N solution of sodium methoxide in methanol (63 ml, 0.063 mol) with stirring at ice-bath temperature. After stirring had been continued for 6 h at room temperature, deposited sodium chloride was filtered off. The solvent was removed under reduced pressure and isopropyl ether was added to the residue. After filtration, the solvent was removed and the oily residue was fractionally distilled *in vacuo* to give a liquid (6.1 g), bp 105—112°C (0.3 mmHg). The distillate was further purified by column chromatography on silica gel using $CHCl_3$ as an eluent to give 4.5 g (60%) of **2**, bp 92—93°C (0.05 mmHg). *Anal.* Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.81; H, 8.00. IR $\nu_{max}^{liq.}$ cm^{-1}: 1732 (C=O). PMR δ: 0.95 (3H, d, J=6 Hz, CH_3), 2.35, 2.85 (each 1H, dd, J=18, 6 Hz, CH_2), 3.66 (1H, sext, J=6 Hz, >CH–), 3.16, 3.19, 3.25 (each 3H, s, $3\times CH_3O$), 7.25—7.64 (5H, m, C_6H_5).

2-Isopropylidene-4-pentenoic Acid Methyl Ester (4)——4,4-Dichloro-2-methyl-6-hepten-3-one (3) (5.85 g, 0.03 mol) was added to a 2 N solution of sodium methoxide in methanol (31.5 ml, 0.063 mol) with stirring at ice-bath temperature. After stirring had been continued for 2 h at room temperature, deposited sodium chloride was filtered off. The solvent was removed under reduced pressure and isopropyl ether was added to the residue. After filtration, the solvent was removed and the oily residue was fractionally distilled *in vacuo* to give 2.8 g (61%) of **4**, bp 112—117°C (77 mmHg). An analytical sample was obtained by silica gel column chromatography using hexane–benzene as an eluent. Yield, 2.2 g (48%); bp 101—102°C (55 mmHg). *Anal.* Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.19; H, 9.04. IR $\nu_{max}^{liq.}$ cm^{-1}: 1722 (C=O), 1641 (C=C). PMR δ: 1.81, 2.01 (each 3H, s, $2\times CH_3$), 3.01 (2H, br d, J=6 Hz, CH_2), 3.70 (3H, s, CH_3O), 4.75—5.15 (2H, m, =CH_2), 5.45—6.10 (1H, m, –CH=).

2-Isopropylidene-4-pentenoic Acid (5)——A solution of 4,4-dichloro-2-methyl-6-hepten-3-one (3) (9.8 g, 0.05 mol) in dioxane (20 ml) was added to a solution of sodium hydroxide (12.0 g, 0.3 mol) in water (30 ml) and the mixture was heated under reflux for 1 h with vigorous stirring. After cooling, the aqueous layer was separated and the dioxane layer was washed with conc. NaOH solution. The combined aqueous solution was acidified with 20% H_2SO_4 and the liberated oil was extracted with isopropyl ether. The extract was dried over $MgSO_4$ and concentrated, and the residue was fractionally distilled *in vacuo* to give 3.3 g (47%) of **5**, bp 123—125°C (15 mmHg). *Anal.* Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.46; H, 8.67. IR $\nu_{max}^{liq.}$ cm^{-1}: 1686 (C=O), 1640 (C=C), 1628 (C=C), 2900 (OH). PMR δ: 1.90, 2.17 (each 3H, s, $2\times CH_3$), 3.13 (2H, br d, J=6 Hz, CH_2), 4.80—5.20 (2H, m, =CH_2), 5.55—6.15 (1H, m, –CH=), 11.35 (1H, br s, OH).

1,1,1-Trichloro-2-hexadecanol (8)——A mixture of 1-tetradecene (6) (39.3 g, 0.2 mol), chloral (35.4 g, 0.24 mol) and anhydrous ferric chloride (1.6 g, 0.01 mol) was stirred at room temperature for 7 h. The reaction mixture was dissolved in isopropyl ether (100 ml) and the solution was washed with 5% H_2SO_4 (2×100 ml) and dried over $MgSO_4$. Removal of the solvent left crude 1,1,1-trichloro-4-hexadecen-2-ol (**7**) (70 g) as a liquid. A mixture of crude **7** (17.2 g, 0.05 mol) and 10% Pd–C (0.8 g) in ethanol (30 ml) was shaken with hydrogen at atmospheric pressure until uptake of hydrogen had ceased (10 h). The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. Fractional distillation of the residue *in vacuo* gave 11.1 g (64% from **6**) of **8**, bp 155—160°C (0.1 mmHg). An analytical sample was obtained by silica gel column chromatography using hexane–benzene as an eluent; bp 157—158°C (0.15 mmHg), mp 23—24°C. *Anal.* Calcd for $C_{16}H_{31}Cl_3O$: C, 55.58; H, 9.04. Found: C, 55.65; H, 8.93. IR ν_{max}^{KBr} cm^{-1}: 3430 (OH). PMR δ: 0.86 (3H, t, J=5.5 Hz, CH_3), 1.25 (26H, br s, $13\times CH_2$), 2.95 (1H, br d, J=6 Hz, OH), 4.00 (1H, m, >CH).

1,1,1-Trichloro-2-(2-propenoxy)hexadecane (9)——A solution of sodium hydroxide (2.4 g, 0.06 mol) in water (4 ml) was added to a solution of 1,1,1-trichloro-2-hexadecanol (**8**) (7.0 g, 0.02 mol), allyl bromide (3.6 g, 0.03 mol) and tetrabutylammonium iodide (0.36 g, 0.001 mol) in benzene (10 ml). The mixture was vigorously stirred at room temperature for 2 h. The organic layer was separated and the aqueous layer was extracted with benzene. The combined benzene solution was washed with brine and dried over $MgSO_4$. The solvent was removed and the oily residue was distilled *in vacuo* to give 5.6 g (73%) of **9**, bp 165—167°C (0.13 mmHg). An analytical sample was obtained by silica gel column chromatography using hexane as an eluent; bp 184—185°C (0.4 mmHg). *Anal.* Calcd for $C_{19}H_{35}Cl_3O$: C, 59.14; H, 9.14. Found: C, 59.57; H, 9.14. IR $\nu_{max}^{liq.}$ cm^{-1}: 1650 (C=C), 1113 (C–O). PMR δ: 0.86 (3H, t, J=5.5 Hz, CH_3), 1.25 (26H, br s, $13\times CH_2$), 3.75 (1H, dd, J=8, 3 Hz, >CH–), 4.05—4.70 (2H, m, CH_2), 5.05—5.45 (2H, m, =CH_2), 5.67—6.30 (1H, m, –CH=).

4,4-Dichloro-1-nonadecen-5-one (11)——1,1,1-Trichloro-2-(2-propenoxy)hexadecane (**9**) (5.0 g, 0.013 mol) was added to a stirred solution of potassium *tert*-butoxide (2.6 g, 0.023 mol) in tetrahydrofuran (26 ml) at ice-bath temperature. The resulting solution was stirred at 0°C for 2 h and at room temperature for an additional 2 h. Excess *tert*-butoxide was quenched by passing CO_2 through the reaction mixture. After removal of the solvent, the residue was extracted with isopropyl ether. The extract was dried over $MgSO_4$, and removal of the solvent gave 4.0 g of crude 1,1-dichloro-2-(2-propenoxy)-1-hexadecene (**10**). The dichlorovinyl ether **10** was heated at 120—130°C for 0.5 h. The resulting liquid was distilled *in vacuo* to give 3.5 g (77%) of dichloroketone **11**, bp 155—157°C (0.2 mmHg). An analytical sample was obtained by silica gel column chromatography using hexane as an eluent; bp 153—154°C (0.15 mmHg). *Anal.* Calcd for $C_{19}H_{34}Cl_2O$: C, 65.32; H, 9.81. Found: C, 65.74; H, 9.71. IR $\nu_{max}^{liq.}$ cm^{-1}: 1734 (C=O), 1644 (C=C). PMR δ: 0.88 (3H, t, $J=5.5$ Hz, CH_3), 1.25 (24H, br s, $12\times CH_2$), 2.92 (2H, t, $J=7$ Hz, CH_2CO), 3.08 (2H, br d, $J=6$ Hz, CH_2), 5.05—5.40 (2H, m, $=CH_2$), 5.60—6.30 (1H, m, –CH=).

5-Iodomethyl-3-tetradecanylidenedihydro-2(3*H*)-furanone (13a: *Z* Isomer, 13b: *E* Isomer)——A solution of 4,4-dichloro-1-nonadecen-5-one (**11**) (2.3 g, 6.6 mmol) in dioxane (3 ml) was added to a solution of sodium hydroxide (1.6 g, 40 mmol) in water (4 ml), and the mixture was heated under reflux with stirring for 1 h. After cooling, the reaction mixture was acidified with 20% H_2SO_4 and a liberated oil was extracted with isopropyl ether. The extract was dried over $MgSO_4$, and removal of the solvent left a mixture of *E* and *Z* forms of crude 2-(2-propenyl)-2-hexadecenoic acid (**12**) as a liquid (2.0 g). The crude mixture **12** (1.8 g, 6.1 mmol) was neutralized with excess potassium bicarbonate (1.8 g, 18.3 mmol) in water (10 ml). Ether (4 ml) and iodine (1.7 g, 6.7 mmol) were added to the mixture in small portions. The mixture was stirred for 2 h at room temperature, then excess iodine was quenched by addition of $Na_2S_2O_4$ solution. The reaction mixture was extracted with ether and the ethereal extract was dried over $MgSO_4$. Removal of the solvent left an oil, which was column-chromatographed on silica gel using hexane–benzene as an eluent to give 0.73 g (31% from **11**) of **13a** and 0.56 g (24% from **11**) of **13b**.

13a: Prisms (hexane), mp 39—40°C. *Anal.* Calcd for $C_{19}H_{33}IO_2$: C, 54.29; H, 7.91. Found: C, 54.72; H, 7.87. IR ν_{max}^{KBr} cm^{-1}: 1763 (C=O), 1670 (C=C). PMR δ: 0.88 (3H, t, $J=5.5$ Hz, CH_3), 1.25 (22H, br s, $11\times CH_2$), 2.47—2.87 (2H, m, CH_2), 2.95—3.50 (4H, m, CH_2I, CH_2), 4.38—4.66 (1H, m, –OCH<), 6.14—6.33 (1H, m, –CH=).

13b: Prisms (hexane), mp 44.5—45.5°C. *Anal.* Calcd for $C_{19}H_{33}IO_2$: C, 54.29; H, 7.91. Found: C, 54.76; H, 7.98. IR ν_{max}^{KBr} cm^{-1}: 1746 (C=O), 1682 (C=C). PMR δ: 0.88 (3H, t, $J=5.5$ Hz, CH_3), 1.26 (22H, br s, $11\times CH_2$), 2.03—2.35 (2H, m, CH_2), 2.41—3.54 (4H, m, CH_2I, CH_2), 4.43—4.71 (1H, m, —OCH<), 6.64—6.87 (1H, m, –CH=).

5-Methylene-(*Z*)-3-tetradecanylidenedihydro-2(3*H*)-furanone (or Deoxyobtusilactone A) (14)——A solution of DBU (1.52 g, 10 mmol) in isopropyl ether (10 ml) was added dropwise to a stirred solution of iodolactone **13a** (0.42 g, 1 mmol) in isopropyl ether (5 ml) at −20°C. The mixture was stirred at −20°C for 2 h and at 0°C for an additional 5 h. Excess DBU was quenched by passing CO_2 through the reaction mixture and the resulting precipitate was filtered off. After removal of the solvent, the residue was column-chromatographed on silica gel using hexane–isopropyl ether (5%) as an eluent to give 21 mg (7%) of **14** as crystals, mp 43—44°C. *Anal.* Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.55; H, 10.93. MS *m/e*: 292 (M^+), 249, 235, 221, 207, 193, 179, 165, 151, 137. IR ν_{max}^{KBr} cm^{-1}: 1782 (C=O), 1682 (C=C), 1666 (C=C). PMR δ: 0.88 (3H, t, $J=5.5$ Hz, CH_3), 1.26 (22H, br s, $11\times CH_2$), 2.71 (2H, br q, $J=8$ Hz, CH_2), 3.46—3.58 (2H, m, CH_2), 4.20—4.27, 4.67—4.75 (each 1H, m, $=CH_2$), 6.27 (1H, tt, $J=8$, 2 Hz, =CH–). CMR δ: 14.09 (q, CH_3), 22.70 (t, CH_2), 28.07, 28.99, 29.37, 29.64, 31.91 (t, CH_2), 87.66 (t, $=CH_2$), 122.45 (s, $=\overset{|}{C}-$), 145.86 (d, –CH=), 153.06 (s, $O-\overset{|}{C}=$), 167.20 (s, C=O). Subsequent elution gave 226.7 mg (54%) of recovered **13a**.

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References and Notes

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7) All boiling and melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi EPI-G2 spectrophotometer. PMR and CMR spectra were obtained with a Hitachi R-24 spectrometer and a JEOL JNM-FX-90-Q spectrometer in $CDCl_3$. Chemical shift values are given in δ (ppm) relative to tetramethylsilane as an internal standard. The following abbreviations are used: s, singlet; d, doublet; t, triplet; sext, sextet; m, multiplet; br, broad; dd, doublet of doublets; tt, triplet of triplets. Mass spectra (MS) were recorded with a Hitachi RMS-4 spectrometer.