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Synthesis of Racemic Loliolide

Zen-ichi Horii, Takane Yagami, Masayoshi Ito, and Miyoji Hanaoka

Faculty of Pharmaceutical Sciences, Osaka University[1]

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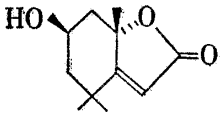
Racemic loliolide (XIII) and its diastereoisomer (XI) were synthesized from 2-bromo-2,6,6-trimethylcyclohexanone (II). The syntheses provide unequivocal confirmation for the proposed structure (I).

Loliolide was isolated from *Lolium perenne*[2,3] and assigned the structure I.[2] On the other hand digiprolactone,[4] isolated from *Digitalis purpurea*, was independently established the structure as I and confirmed to be identical with loliolide which was also isolated from *Fumaria officinalis*[5] and *Digitalis lanata*.[6] In a previous short communication,[7] we have already reported the synthesis of racemic loliolide, which has corroborated the proposed structure. The present paper is concerned with a full account of the experiments. Recently another synthesis of racemic loliolide in a different route was reported.[8]



I

Chart 1

Dehydrobromination of 2-bromo-2,6,6-trimethylcyclohexanone (II)[9] with lithium bromide and lithium carbonate in dimethylformamide gave the α,β-unsaturated ketone (III)[10] in 91% yield. Allylic bromination of III with N-bromosuccinimide afforded the bromoketone (IV), which was heated with silver acetate in benzene to give the acetoxy-ketone (V) in 75% yield. Hydrogenation of V over 5% palladized charcoal in ethanol yielded the desired saturated ketone (VI)[11] having absorptions at 1736 and 1709 cm^{-1} in the infrared spectrum in 50% yield, together with 2,6,6-trimethylcyclohexanone (VII), which was assumed to be obtained by hydrogenolysis of V and identified with an authentic specimen.[9]

Bromination of VI in acetic acid in the presence of hydrobromic acid furnished the acetoxybromoketone (VIII), mp 73—74°, in 76% yield. The structure of VIII was verified by its spectral evidences: absorptions at 1745 and 1709 cm^{-1} in the infrared spectrum; a proton resonance peak at C_4 in the nuclear magnetic resonance (NMR) spectrum[12] at 4.43τ as a heptet with coupling constants (J=5.0 and 10.0 cps) due to an axial proton.[13] Thus the stereochemistry of the product should be represented by VIII, if the cyclohexane ring is assumed to be in the chair conformation. Treatment of VIII with sodium methoxide in absolute methanol

1) Location: *Toneyama, Toyonaka, Osaka-fu.*
2) R. Hodges and A.L. Porte, *Tetrahedron*, **20**, 1463 (1964).
3) E.P. White, *New Zealand J. Agric. Res.*, **1**, 859 (1958).
4) *a*) D. Satoh, H. Ishii, Y. Oyama, T. Wada, and T. Okumura, *Chem. Pharm. Bull.* (Tokyo), **4**, 284 (1956). *b*) T. Wada and D. Satoh, *ibid.*, **12**, 752 (1964). *c*) T. Wada, *ibid.*, **12**, 1117 (1964). *d*) *Idem, ibid.*, **13**, 43 (1965).
5) R.H.F. Manske, *Can. J. Res.*, **B16**, 438 (1938).
6) R. Tschesche and G. Buschauer, unpublished, *cf.* references 3), 4*d*).
7) Z. Horii, T. Yagami, and M. Hanaoka, *Chem. Commun.*, 634 (1966).
8) J.N. Marx and F. Sondheimer, *Tetrahedron*, Suppl. 8, Part I, 1 (1966).
9) C.L. Stevens and A.J. Weinheimer, *J. Am. Chem. Soc.*, **80**, 4072 (1958).
10) J. Meinwald and C.C. Cornwall, *J. Am. Chem. Soc.*, **77**, 5991 (1955).
11) *cf.* F. Hoffman-LaRoche & Co. Akt.-Ges., Brit. Patent 790607 (*C.A.*, **52**, 15575*d* (1958)).
12) The NMR spectra were measured on Hitachi Perkin-Elmer H-60 type Spectrometer at 60 mc in $CDCl_3$ with tetramethylsilane as an internal reference.
13) N.S. Bhacca and D.H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, 1964, p. 77.

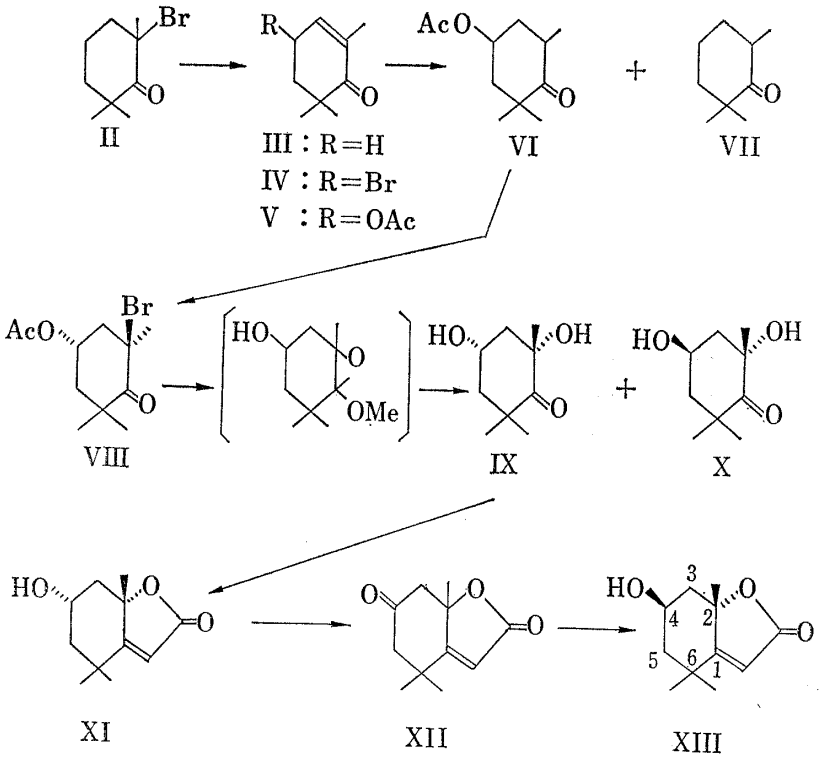


Chart 2

afforded the epoxide with the absence of carbonyl bands in the infrared spectrum. Hydrolysis of the crude epoxide with aqueous methanol containing a few drops of dilute sulfuric acid yielded a mixture of two diastereoisomers of 2,4-dihydroxy-2,6,6-trimethylcyclohexanone, which was separable into pure components (IX), mp 65—67°, and (X), mp 90—90.5°, by chromatography on silica gel, in 39% and 6% yields respectively.

We have been interested in the condensation of α-ketol (XIV) with lithium ethoxyacetylide[14] and the subsequent treatment with acid into α,β-butenolide (XV) in a fair yield.[15] According to this procedure, the main product dihydroxy-ketone (IX) was condensed with lithium ethoxyacetylide in anhydrous ether at −30°. Treatment of the resulting crude carbinol with dilute sulfuric acid in tetrahydrofuran afforded the butenolide (XI), mp 80.5—82°, in 34% yield. In agreement with structure XI, the product exhibited absorptions at 3571, 3425, 1741, 1629 and 866 cm^{-1} in the infrared spectrum and at 213 mμ in the ultraviolet spectrum. Its NMR spectrum showed a peak at 5.85τ as a triplet of triplets due to an axial proton[13] at C_4. For loliolide has been reported to have an equatorial proton at C_4,[2,4d] the butenolide (XI) must be a diastereoisomer of loliolide. This conclusion also leads to the establishment of the stereochemistries of dihydroxy-ketones, (IX) and (X), described above, namely two hydroxyl groups in IX are *cis* to each other and those of X are *trans*.

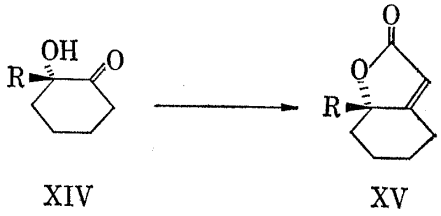


Chart 3

It has been reported[4d] that the keto-lactone, derived from loliolide by Jones oxidation, could be reduced stereoselectively into loliolide with sodium borohydride. Accordingly, oxi-

14) J.F. Arens, "Advances in Organic Chemistry Methods and Results," Vol. II, Interscience, New York, 1960, p. 203.

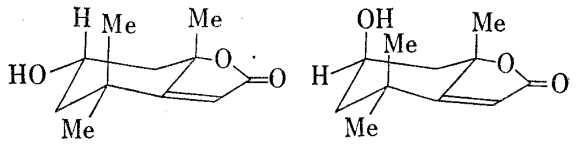
15) Z. Horii, M. Hanaoka, Y. Tamura, S. Saito, and N. Sugimoto, *Chem. Ind.* (London), 664 (1964); Z. Horii, M. Hanaoka, Y. Yamawaki, Y. Tamura, S. Saito, N. Shigematsu, K. Kotera, H. Yoshikawa, Y. Sato, H. Nakai, and N. Sugimoto, *Tetrahedron*, **23**, 1165 (1967).

dation of the butenolide (XI) with Jones reagent gave the keto-lactone (XII), mp 69—70°, which was reduced with sodium borohydride in methanol to afford racemic loliolide (XIII), mp 138—139°, in 85% overall yield. The product showed absorptions at 3585, 3418, 1736, 1626 and 865 cm^{-1} in the infrared spectrum and at 213 mμ in the ultraviolet spectrum. In the NMR spectrum, a proton at C_4 appeared at 5.63τ as a quintet due to an equatorial proton.[13] The synthetic racemic loliolide was shown to be identical with natural loliolide in the infrared and ultraviolet spectra and in retention time in gas-liquid chromatography.[16,17]

Table I. The NMR Spectra of Racemic Loliolide (XIII) and Its Diastereoisomer (XI) (τ-value)

Compound	C-Methyl	=CH	CHOH
XI	8.72 s, 8.68 s, 8.41 s	4.27 s	5.85 t-t (J=11.8, 3.7)
XIII	8.69 s, 8.49 s, 8.17 s	4.27 s	5.63 q (J=3.6)

s: singlet t-t: triplet of triplets q: quintet J: in cps



XIa XIIIa

Chart 4

The stereochemistry of loliolide (I) is supported by the comparison of the NMR spectra of racemic loliolide (XIII) and its diastereoisomer (XI). As mentioned above, a proton at C_4 of XIII resonated as a quintet at lower field than did that of XI as a triplet of triplets. Further more two of the methyl signals in XIII were shifted to the lower field than those in XI. These data indicate the 1,3-diaxial relationship[18] of hydroxyl group at C_4 and two methyl groups at C_2 and C_6 of XIII as well as a chair conformation of the cyclohexane ring. The stereochemistries of XI and XIII are thus those depicted in XIa and XIIIa respectively.

Experimental

Melting points and boiling points are uncorrected. The extracts were dried over Na_2SO_4 unless otherwise specified.

2,6,6-Trimethyl-2-cyclohexenone (III)——To a solution of II[9] (8.7 g) in dimethylformamide (100 ml) was added LiBr (5.5 g) and Li_2CO_3 (7.9 g) and the mixture was heated at 120° under stirring in a stream of N_2 for 2 hr. The cooled reaction mixture was poured into ice water and extracted with ether. The ether layer was washed with 10% HCl and water. Evaporation of the dried extract and distillation of the residue yielded the unsaturated ketone (III, 5.0 g (91%)) as a colorless oil, bp 62—64° (12 mm Hg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1669 (unsaturated ketone), 873 (double bond). The 2,4-dinitrophenylhydrazone was recrystallized from EtOH as red needles, mp 153—154°. *Anal.* Calcd. for $C_{15}H_{18}O_4N_4$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.51; H, 5.78; N, 17.72.

4-Bromo-2,6,6-trimethyl-2-cyclohexenone (IV)——A solution of III (6.5 g) in anhydrous CCl_4 (30 ml) was refluxed with N-bromosuccinimide (8.2 g) in the presence of a small amount of benzoyl peroxide until N-bromosuccinimide was completely converted into succinimide. The succinimide formed was filtered off and the filtrate was evaporated. Distillation of the residue yielded the bromo-ketone (IV, 8.8 g (86%)) as a yellow oil, bp 95—98° (7 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1675 (unsaturated ketone), 1631 sh, 863 (double bond). *Anal.* Calcd. for $C_9H_{13}OBr$: C, 49.81; H, 6.04. Found: C, 49.54; H, 5.99.

4-Acetoxy-2,6,6-trimethyl-2-cyclohexenone (V)——A solution of IV (8.8 g) in anhydrous benzene (75 ml) was stirred with AgOAc (13.6 g) at room temperature for 3 hr and then at 60° for 3 hr. After cooling, the

16) Gas-liquid chromatography was carried on Perkin-Elmer gas chromatograph model 800, employing SE-30 column (column temperature 150°).
17) The NMR spectrum of racemic loliolide was identical with published one[2] of active loliolide.
18) Y. Kawazoe, Y. Sato, M. Natsume, H. Hasegawa, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **10**, 338 (1962).

precipitate was filtered and washed with benzene. The combined benzene layers were washed with aqueous $NaHCO_3$ solution and water. Evaporation of the dried benzene layer and distillation of the residue yielded the acetoxy-ketone (V, 6.9 g (87%)) as a pale yellow oil, bp 119—122° (15 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1736, 1233 (acetoxyl), 1678 (unsaturated ketone), 1637, 859 (double bond). *Anal.* Clacd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 66.74; H, 8.23.

4-Acetoxy-2,6,6-trimethylcyclohexanone (VI) and 2,6,6-Trimethylcyclohexanone (VII)——Compound V (5.0 g) was hydrogenated in EtOH (100 ml) over 5% Pd–C (1.5 g) at atmospheric pressure and room temperature. After the cessation of H_2 uptake, the catalyst was filtered off and the filtrate was evaporated. Distillation of the residue yielded two oily fractions, bp 65—67° (14 mmHg) and bp 125—127° (14 mmHg). The lower boiling fraction (VII, 1.4 g (35%)) was identified with authentic specimen.[9] The higher boiling fraction (VI, 2.5 g (50%)) was the desired ketone. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1736, 1241 (acetoxyl), 1709 (ketone). *Anal.* Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.50; H, 9.27.

4-Acetoxy-2-bromo-2,6,6-trimethylcyclohexanone (VIII)——A solution of Br_2 (1.3 g) in AcOH (3 ml) was added dropwise to an ice-cooled solution of VI (1.6 g) in AcOH (3 ml) containing one drop of 48% HBr with stirring. After the color of Br_2 disappeared, water (15 ml) was added to the reaction mixtutre with continued stirring and cooling. The mixture was extracted with ether and the extract was washed with aqueous $NaHCO_3$ solution and water. Evaporation of the dried extract and chromatography of the residue on alumina with benzene gave the crystals, which were recrystallized from *n*-hexane to yield the bromo-ketone (VIII, 1.7 g (76%)) as colorless needles, mp 73—74°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1745, 1239 (acetoxyl), 1709 (ketone). NMR τ: 8.79 (3H, singlet, C–Me), 8.39 (3H, singlet, C–Me), 8.09 (3H, singlet, C–Me), 7.89 (3H, singlet, $-OCOCH_2$), 4.43 (1H, heptet, J=5.0, 10.0 cps, –CHOAc). *Anal.* Calcd. for $C_{11}H_{17}O_3Br$: C, 47.69; H, 6.19. Found: C, 48.03; H, 6.37.

2,4-Dihydroxy-2,6,6-trimethylcyclohexanone (IX) and (X)——To an ice-cooled solution of Na (0.6 g) in absolute MeOH (13 ml) was added VIII (3.7 g) dropwise. The reaction mixture was allowed to stand at room temperature for 24 hr, diluted with water (50 ml), extracted with ether and dried over anhydrous K_2CO_3. Evaporation of the extract gave the crude epoxide (2.2 g), which was added dropwise to 65% MeOH (5.5 ml) containing a few drops of conc. H_2SO_4. Water (4 ml) was added and the reaction mixture was allowed to stand at room temperature for 1 hr and diluted with water (20 ml). The mixture was made alkaline with aqueous KOH solution, saturated with NaCl and extracted with ether. The dried extract was evaporated and the residue (1.9 g) was chromatographed on silica gel (20 g). Elution with $CHCl_3$ gave crystals, which were recrystallized from petroleum benzine–acetone to yield the dihydroxyketone (IX, 0.9 g (39%)) as colorless needles, mp 65—67°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3571, 3460 (hydroxyl), 1701 (ketone). NMR τ: 8.77 (3H, singlet, C–Me), 8.73 (3H, singlet, C–Me), 8.55 (3H, singlet, C–Me), 5.69 (1H, heptet, J=4.8, 9.6 cps, –CHOH). *Anal.* Clacd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.95; H, 9.27. Elution with AcOEt gave crystals, which were recrystallized from petroleum benzine–acetone to yield the dihydroxy-ketone (X, 0.14 g (6%)) as colorless needles, mp 90—90.5°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3559, 3413 (hydroxyl), 1701 (ketone). NMR τ: 8.78 (3H, singlet, C–Me), 8.70 (3H, singlet, C–Me), 8.58 (3H, singlet, C–Me), 5.61 (1H, heptet, J=4.7, 9.4 cps, –CHOH). *Anal.* Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.85; H, 9.15.

2,4-Dihydroxy-2,6,6-trimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid γ-Lactone (XI)——A solution of ethoxyacetylene[19] (1.8 g) in anhydrous ether (8 ml) was added to a stirred solution of MeLi (prepared from Li (0.36 g) and MeI (3.6 g)) in anhydrous ether (15 ml) in a stream of N_2 at −15° over a period of 10 min. The reaction mixture was stirred for an additional 15 min. To the mixture was added a solution of IX (0.9 g) in anhydrous ether (10 ml) at −25°——30° under stirring over a period of 30 min. After the addition was complete, stirring was continued for 2 hr at −30° and 3 hr at room temperature. The resulting complex was decomposed with saturated aqueous NH_4Cl solution. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layers were dried and evaporated to give a reddish brown oil (1.0 g). A solution of this oil in tetrahydrofuran (17.5 ml) was refluxed with 15% H_2SO_4 (2.5 ml) for 15min. The solution was neutralized with $NaHCO_3$, evaporated, and extracted with $CHCl_3$. Evaporation of the dried extract and chromatography of the residue (1.0 g) on silica gel (10 g) with $CHCl_3$ gave crystals, which were recrystallized from petroleum benzine–AcOEt to yield the butenolide (XI, 0.3 g (34%)) as colorless needles, mp 80.5—82°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3571, 3425 (hydroxyl), 1741 (unsaturated γ-lactone), 1629, 866 (double bond). UV λ_{max}^{EtOH} $m\mu$ (log ε): 213 (4.24). *Anal.* Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.26; H, 8.25.

2-Hydroxy-4-oxo-2,6,6-trimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid γ-Lactone (XII)——To a stirred solution of XI (100 mg) in acetone (1.5 ml) was added Jones reagent (0.2 ml) at room temperature. After 7 min, the solution was diluted with water and extracted with AcOEt. The extract was washed with water and dried. The solvent was removed and the residue was recrystallized from petroleum ether yielded the keto-lactone (XII, 85 mg (85%)) as colorless needles, mp 69—70°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1764 (unsaturated γ-lactone), 1721 (ketone), 1631, 865 (double bond). NMR τ: 8.68 (3H, singlet, C–Me), 8.56 (3H, singlet, C–Me), 8.39

19) E.R. Jones, G. Eglinton, M.C. Whiting, and B.L. Shaw, "Organic Syntheses," **34**, Wiley, New York, 1954, p. 46.

(3H, singlet, C-Me), 7.53 (2H, singlet, CH_2), 7.04, 7.31 (2H, AB quartet, $J=13.8$ cps, CH_2), 4.04 (1H, singlet, =CH). *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.08; H, 7.29.

Racemic Loliolide (XIII)——To a stirred solution of XII (100 mg) in MeOH (8ml) was added $NaBH_4$ (50 mg) at 0°. The mixture was stirred for 1 hr, diluted with water and extracted with ether. The extract was washed with water and dried. Evaporation of the extract and recrystallization of the residue from CCl_4 yielded racemic loliolide (XIII, 100 mg (100%)) as colorless needles, mp 138—139°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3585, 3418 (hydroxyl), 1736 (unsaturated γ-lactone), 1626, 865 (double bond). UV λ_{max}^{EtOH} $m\mu$ (log ε): 213 (4.17). *Anal.* Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.06; H, 8.03.

This product was identical with natural loliolide in IR ($CHCl_3$), UV and in retention time in gas-liquid chromatography.

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