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STUDIES ON THE SESQUITERPENOIDS OF *HYPOLEPIS PUNCTATA* METT.—II

THE TOTAL SYNTHESIS OF HYPACRONE

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Abstract—Hypacrone (**1**), a new seco-illudoid, was synthesized by several steps, including a cross aldol condensation of two major moieties, a diketone (**2**) and a cyclopentenone derivative (**11**).

Hypacrone is a novel seco-illudoid isolated and the acrid principle of a fern, *Hypolepis punctata* Mett.[1] This paper details the total synthesis of hypacrone[2] and some analogous compounds.

The synthesis was envisaged as the linking of two major synthons, C_7 and C_8 in the formula **1**, with the formation of a [Z]-6,7-double bond.

For the C_7 unit, 1,1-diacetylcyclopropane (**2**) or its mono-ethylene ketal (**3**), was adopted and was readily prepared[11] from acetylacetone and ethylene by means of mercuric acetate.

Prior to the synthesis of the C_8 unit, the reactivity of compounds, **2** and **3**, was examined in the Wittig reaction, as a method for completing the [Z]-6,7-double bond.[3] However, both compounds were not sufficiently reactive even under forcing conditions. The second choice was the use of organometallic reagents prepared from the C_8 unit. For this purpose, two iodomethylcyclopentanone derivatives, (**4** and **5**), were synthesized (see below). In this approach the expected geometry of the 6,7-double bond could be [E], because it was introduced by dehydration of a carbinol precursor. However, the double bond would be isomerized to the [Z]-orientation at any of the later steps.

When the iodo-compound (**4**) was reacted with the half ketal (**3**) by the action of metallic lithium and subsequently hydrolyzed with acid, a 70% yield of a condensation product (**6**) was obtained which dehydrated on pyrolysis at 240° to give a mixture of olefins, (**7** and **8**), separable by preparative layer chromatography. A diol (**7a**), obtained by acid hydrolysis of **7**, gave a monotosylate (**7b**) as a single product with one equivalent of tosyl chloride.

On the other hand, the reaction of the other iodocyclopentanone (**5**) with the half ketal (**3**) also afforded a keto-diol (**9**). This compound (**9**), on Jones' oxidation followed by pyrolytic dehydration, gave an ene-dione (**10**), which was regarded as dihydrohypacrone.† Unfortunately, further conversion of the intermediate, **7a**, **7b** or **10**, into hypacrone was not successful.

The next effort was to find an effective method for linking another C_8 unit already equipped with all functions corresponding to those of hypacrone, since transformations on the cyclopentane ring did not seem possible after construction of C_{15} skeleton. A cross aldol condensation, recently developed,[4] was promising. Actually, condensation of 3,5,5-trimethylcyclopentenone (**11**) with the diketone (**2**),[4] gave the desired aldol product (**13**), which was successfully changed to hypacrone (**1**).

A lithium dienolate, prepared from **11** and lithium di-isopropylamide, was quenched by trimethylsilyl chloride to form a dienol trimethylsilyl ether (**12**).[13] Compound **12** was so susceptible to hydrolysis, even in neutral conditions, that it could be barely isolated by quick extraction at 0° to ascertain the structure by spectral analysis. The PMR spectrum of the product revealed three olefinic proton signals, which excluded the possibility of the enolization at C-4.‡ The isolation yield of the dienol silyl ether (**12**) was so poor that condensation with the diketone (**2**) was carried out *in situ*.

To a freshly prepared dienol silyl ether solution were added methylene chloride solutions of the diketone (**2**) and titanium tetrachloride, successively, at −78°. A dark brown mixture was worked up as usual to give an expected diketo-carbinol (**13**), in 25% yield (not optimized), which was dehydrated by passing through a gas chromatography column kept at 190°. From the oily mixture, a pure dehydration product (**14**) was isolated by

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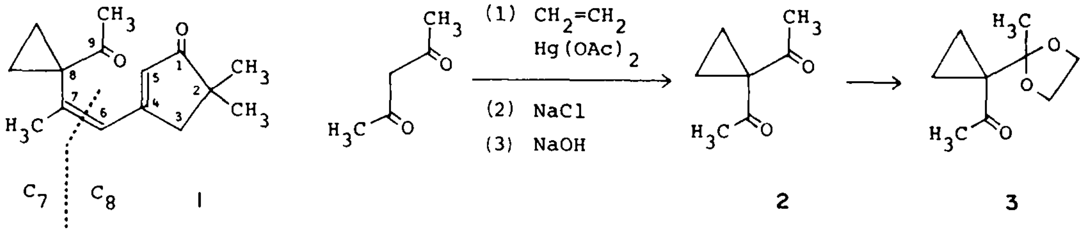
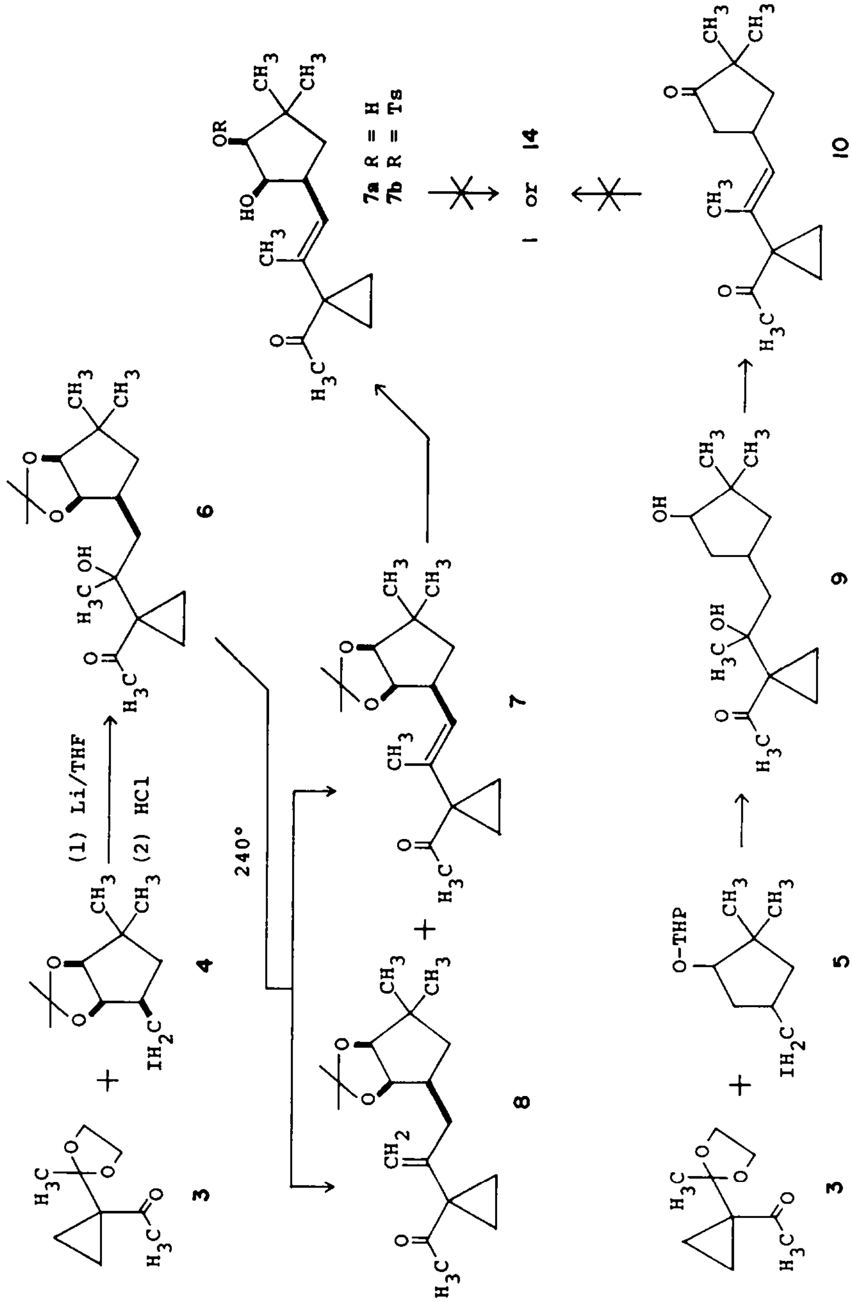
†The geometry of the 6,7-double bond is not obvious.

‡Bromination of the enone (**11**) always proceeded at C-4, in contrast to this kinetically controlled enolate formation by lithium di-isopropylamide.[13]



Scheme 1.



Scheme 2.

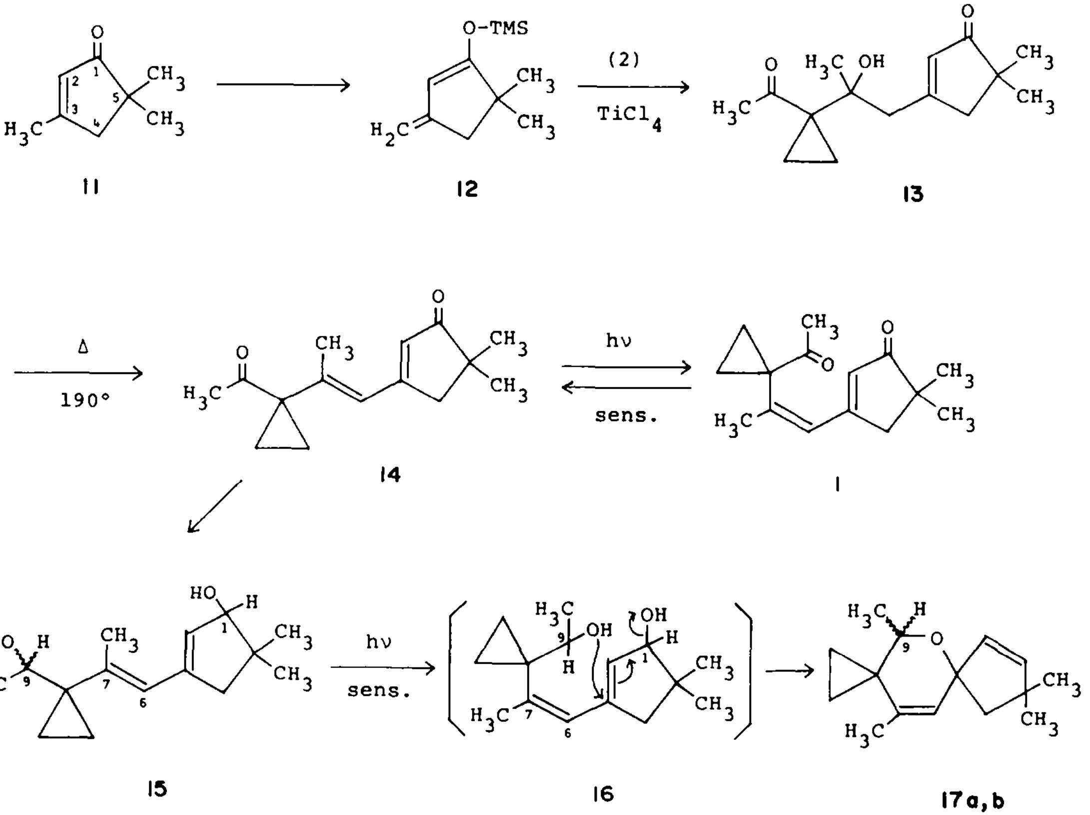
(repeated) preparative layer chromatography. This compound (**14**) showed closely similar properties to those of natural hypacrone in UV, IR and mass spectra. The PMR spectrum showed that each signal of **14** slightly deviated from the corresponding signal of hypacrone in chemical shift values, but the intensity relationship and the splitting pattern of both spectra were almost identical (Fig. 1). It was, therefore, concluded that the compound (**14**) was a geometrical isomer of natural hypacrone about the 6,7-double bond; [Z] in hypacrone and [E] in the compound (**14**). In fact, the latter gave no trace of pterosins under the acidic condition, which changed natural hypacrone to pterosins.[1]

The compound (**14**) was irradiated at 0° in methanol-d$_4$, in the presence of 2-acetonaphthone as a sensitizer, and the reaction was traced by monitoring the PMR spectrum. A group of new signals appeared on the original spectrum of **14** after 30 min irradiation. These new signals were exactly consistent with those of natural hypacrone on comparing the spectra in three different solvents, methanol-d$_4$, carbon tetrachloride and benzene-d$_6$. After 2-hr irradiation, a photo-chemical equilibrium ([Z]:[E] = 46:54) was established. Approximately the same ratio of both isomers was also obtained on irradiation of natural hypacrone under similar conditions.

Separation of [Z]-hypacrone from the equilibrium mixture was rather difficult, since the isomers were indistinguishable (TLC or GLC under various conditions). Chromatography on a fine and long column (2 mm in diameter and 600 mm in length) of neutral alumina overcame this difficulty. When fractions were collected carefully in small portions, the pure [Z]-isomer was eluted in a few fractions at the elution front. Hypacrone thus obtained crystallized on standing (m.p. 48–52°), and was identical with the natural product in IR and NMR spectra. The fractions following those of pure hypacrone were contaminated with increasing amounts of the [E]-isomer. After complete elution of the isomeric hypacrones, some pterosin Z was obtained as fine crystals by washing the column with ether. Possibly, a part of [Z]-hypacrone in the equilibrium mixture was changed to pterosin Z by the catalysis of alumina.

In order to improve the isomerization yield of [E]-hypacrone, the photo-reaction was attempted with the diol **15**: This procedure was analogous to Liu's method[5] for the quantitative conversion of [E]-β-ionol to the [Z]-isomer.

Reduction of the [E]-dione (**14**) with LAH gave an unstable diol (**15**), which decomposed on standing to form a complicated mixture. Immediately after preparation, **15** was irradiated under the same condition as for the dione (**14**). The reaction proceeded quickly and quantitatively and, after 15 min, the diol (**15**) was replaced by a product with a higher R_f value on thin layer chromatography. Absence of the OH group (IR) and the molecular weight estimation (M$^+$ 218) from mass spectrum clearly demonstrated that the new compound was a dehydration product of the original diol (1 mole of water). The PMR spectrum exhibited signals of three olefinic protons (two of them appeared in AB type), two t-Me groups, a sec-Me and a vinylic Me group. Careful analysis of the spectrum in benzene-d$_6$ indicated a mixture (1:1) of two components: an epimeric pair (at C-9) of a tricyclic spiroether (**17**). The stereochemistry of each epimer still remains unclear. In this reaction, a transformation of the double bond geometry (from 6,7-[E] to 6,7-[Z]) analogous to the Liu's result also proceeded under the described condition to form an



Scheme 3.

intermediate (**16**). However, the simultaneous addition of the OH group (at C-9) to the double bond on the cyclopentane ring produced the spiro-ether (**17**), quantitatively, with concomitant removal of the OH group at C-1, as indicated in the scheme.

The C_8 synthons, (**11**, **4** and **5**), were synthesized by the following methods. All intermediates in the preparations were well characterized by spectral and/or elementary analysis.

(1) 3,5,5-*Trimethylcyclopent*-2-*enone* (**11**). This preparation was a modification of Agosta and Smith's procedure[6] for 5,5-dimethylcyclopentenone. The α-lithio derivative of sodium iso-butyrate,[7] prepared from lithium di-isopropylamide and sodium isobutyrate, was treated with methallyl chloride to give 2,2,4-trimethyl-4-pentenoic acid (**18**) in 76% yield. The corresponding acid chloride of **18** was cyclyzed to the trimethylcyclopentenone (**11**) with aluminum chloride in 67% yield. This procedure may be extended to a short-step preparative method of various cyclopentenone derivatives.

(2) *Acetonide of* 5,5 - *dimethyl* - 3 - *iodomethylcyclopentane* - 1,2 - *diol* (**4**). 4,4-Dimethylglutaroin (**19**),[8] prepared from dimethyl 3,3-dimethylglutarate, was converted to an enone (**20**) in 3 steps (88% overall yield).[9] Direct acid catalyzed dehydration[10] of **19** was not satisfactory. The enone (**20**) was changed to a crystalline ketone (**22**) in several steps via an acetoxy-diol (**21**). The ketone (**22**) was converted in 3 steps to a tosylate (**23**) (67% yield from **22**), which afforded the iodomethyl compound (**4**) by the treatment with sodium iodide in acetone. The stereochemistry of three asymmetric centers of **4** and other intermediates in this series was assigned to 1,2-[Z]-2,3-[Z] orientation based on the coupling constant (5–6 Hz) between three methine protons, H-1, H-2 and H-3.

(3) *Tetrahydropyranyl ether of* 2,2 - *dimethyl* - 4 - *iodomethylcyclopentanol* (**5**).† 5,5-Dimethylcyclopentenone (**24**), prepared by Agosta and Smith's method,[6] was treated with potassium cyanide in dimethyl sulfoxide and then hydrolyzed with aqueous sulfuric acid to give a carboxylic acid (**25**). **25** was converted, in 3 steps, to a crystalline tosyloxy ketone (**26**), which gave an oily iodo-ketone (**27**) with sodium iodide. Reduction of the ketone (**27**) with diborane gave a iodo-alcohol, which was changed to the tetrahydropyranol ether (**5**) after protection of the OH group.

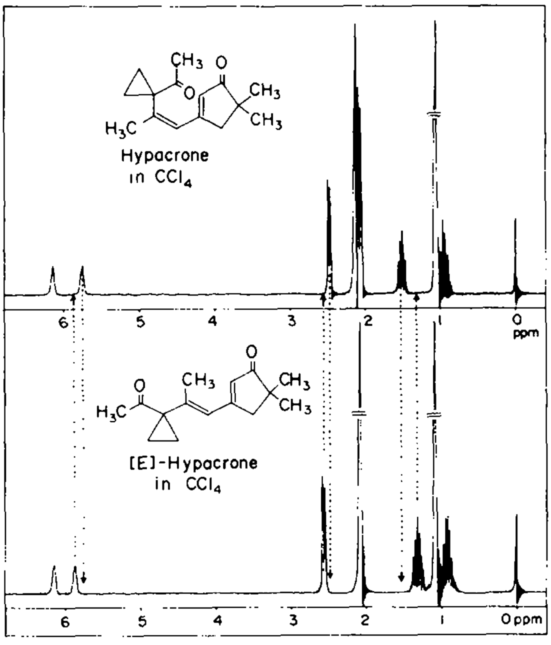


Fig. 1.

Although the preparations of **4** and **5**, as described, appear tedious, the procedures were justified since most of the intermediates were obtained by simple operations and in acceptable yields without any laborious purification.

EXPERIMENTAL

M.ps are uncorrected and were determined on a Yanagimoto micro m.p. apparatus Model MPJ-2. IR spectra were recorded for liquid films or chloroform solns on a Japan Spectroscopic Co. Model IR-E spectrometer, and UV spectra were measured on a Hitachi Model 323 spectrophotometer for EtOH solns. NMR spectra were taken with a JEOL Model PS-100 spectrometer (100 MHz) for chloroform-d or CCl_4 solns using TMS as an internal standard. Mass spectra were measured on a Hitachi Model RMU-6 mass spectrometer. Analytical and preparative gas chromatographies (GLC) were performed by a Shimazu Model 4BMPF and a Varian Model 920 gas chromatograph, respectively, using 5%-SE30 packed column. All organic solvents were purified by distillation with glass joint apparatus before use. Silicagel used for column and thin layer chromatography (TLC) was Merck Kieselgel 60 (70–230 mesh) and Kieselgel GF_{254} (Typ 60), respectively.

1,1-*Diacetylcyclopropane* (**2**). This was prepared[11] from acetylacetone and ethylene with mercuric acetate, followed by the treatment with NaOH, b.p. 78°/14 mm, ν_{max} (neat) 1690 cm^{-1}; $\delta(CCl_4)$ 1.31 (4H, s), 2.06 (6H, s).

Half ketal (**3**) *of* 1,1-*diacetylcyclopropane*. A soln of **2** (2.94 g), 1.51 g (1.2 eq) of ethylene glycol and 60 mg of TsOH in 30 ml benzene was refluxed for 15 hr under continuous removal of water. After working up as suual, a mixture (3.4 g) of 3 components was obtained. The starting diketone (**2**), a half ketal (**3**) and a diketal. Each component was separated by preparative GLC. Half ketal (**3**): ν_{max} (neat) 1690 cm^{-1}; $\delta(CCl_4)$ 0.90 (4H, m), 1.40 (3H, s), 2.16 (3H, s), 3.82 (4H, s).

2,2,4-*Trimethylpent*-4-*enoic acid* (**18**). To a suspension of NaH (50% in oil, 12 g, 0.25 mole) in 25 g (0.25 mole) di-isopropylamine and 80 ml THF a soln of 21 g (0.24 mole) of iso-butyric acid in THF under argon atmosphere was added. After refluxing for 1 hr, the mixture was stirred for 3 hr with 150 ml n-BuLi soln (1.56M in hexane) at room temp. The resulting lithio compound was allowed to react with 24 g (0.26 mole) of methallyl chloride by stirring overnight at 30°. Usual work up of the mixture gave 24 g (76%) of **18**, which was sufficiently pure for the next step. ν_{max} (neat) 3300–2600, 1650, 900 cm^{-1}; $\delta(CCl_4)$ 1.20 (6H, s), 1.70 (3H, br. s), 2.30 (2H, s), 4.63 (1H, m), 4.73 (1H, m), 12.15 (1H, br).

3,5,5-*Trimethylcyclopent*-2-*enone* (**11**). An acid chloride was prepared from 24 g (0.17 mole) of **18**, 38 g (25 ml, 0.3 mole) oxalyl chloride and 100 ml anhyd benzene. A soln of the acid chloride in 40 ml CS_2 was added dropwise to a mixture of powdered $AlCl_3$ (29.5 g, 0.22 mole) in 200 ml CS_2 during 1 hr under vigorous stirring (N_2 atmosphere). After refluxing for 6 hr, the mixture was decomposed with water. A dark brown oil (18 g) obtained as a neutral portion was distilled *in vacuo* to give **11**, 14 g (67%), as a colorless liquid, b.p. 98–100°/40 mm; ν_{max} (neat) 3080, 1700, 1620 cm^{-1}; λ_{max} 228 nm; $\delta(CCl_4)$ 1.04 (6H, s), 2.08 (3H, br s), 2.36 (2H, br s), 5.72 (1H, br s).

Dienonl silyl ether (**12**). To a soln of lithium di-isopropylamide, prepared from di-isopropylamine (202 mg), ether (2 ml) and n-BuLi soln (1.56 M in hexane, 1.5 ml) [0°, 10 min, under Ar atmosphere], a soln of 175 mg of **11** in 1 ml ether was added at 0°. The lithium dienolate soln thus formed was treated at 0° with 217 mg of trimethylsilyl chloride for 1 hr. After decomposition by adding water, the product was quickly taken up in ether at 0°.

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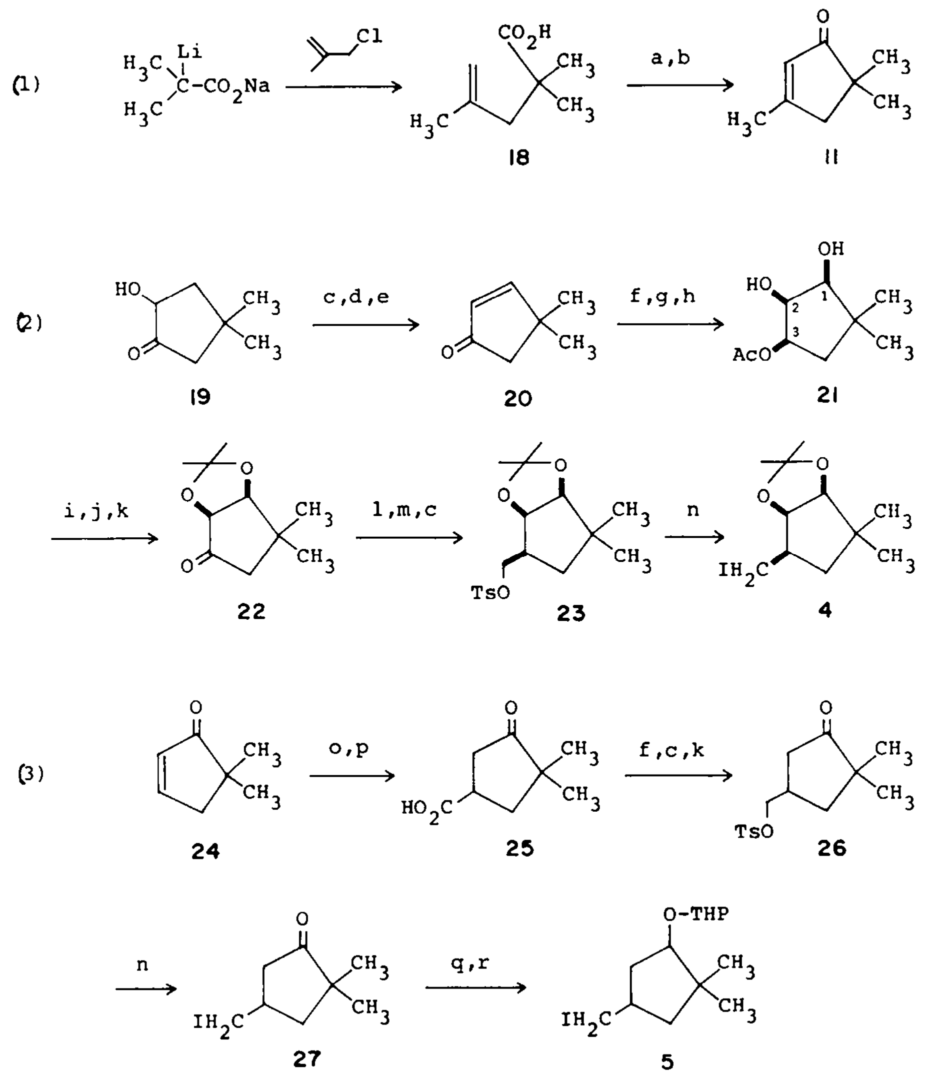
†The stereochemistry of **5** is not obvious; probably, a mixture of two stereoisomers is obtained.



a: $(COCl)_2$, b: $AlCl_3$, c: TsCl-Py, d: $LiCl-Me_2CO$, e: LiBr-DMF,
b: $LiAlH_4$, g: Ac_2O-Py, h: $KMnO_4$, i: $Me_2CO-CuSO_4$, j: NaOH-MeOH,
k: CrO_3-Py, l: $Ph_3P=CH_2$, m: Hydroboration, n: $NaI-Me_2CO$,
o: KCN-DMSO, p: H_2SO_4,· q: BH_3-THF, r: DHP-H^+.

Scheme 4.

A colorless liquid (30 mg, 11%), separated by preparative GLC as a major component, was immediately characterized by determining the spectra, ν_{max} (CCl_4) 3080, 1630, 1605 cm^{-1}; δ(CCl_4) 0.23 (9H, s), 1.03 (6H, s), 2.30 (2H, m), 4.10 (1H, m), 4.22 (1H, m), 4.94 (1H, br. s). The dienol silyl ether was so unstable that most part of the sample dissolved in CCl_4 decomposed on standing for 1 hr after determination of the NMR spectrum.

Condensation of 3,5,5-*trimethylcyclopentenone* (**11**) *with* 1,1-*diacetylcyclopropane* (**2**) *via dienol silyl ether* (**12**). **12** was prepared from di-isopropylamine (3.65 g, 5.1 ml, 36 mmole) in hexane (20 ml), n-BuLi soln (1.56M in hexane, 22 ml, 34 mmole), 3,5,5-trimethylcyclopentenone (4.0 g, 35 mmole) in hexane (20 ml), and trimethylsilyl chloride (7.6 g, 8.7 ml, 70 mmole) as described. To this soln was added dropwise at −78° 4.8 g (35 mmole) of **2** in 20 ml methylene chloride, and then 13.5 g (7.7 ml, 70 mmole) of titanium tetrachloride in 20 ml methylene chloride. After stirring for 3 hr at −78°, the mixture was warmed to room temperature and decomposed with water. Extraction with ether gave 9.2 g of a brown liquid, which was chromatographed on silicagel. Fractions eluted by hexane:ether (1:1) were collected and further purified by preparative TLC (chloroform:ether = 3:1) to afford 1.92 g (25% from **11**) of **13**; MS (70 eV) *m/e* 250 (M^+), 232 (M^+-H_2O), 217 ($M^+-H_2O-CH_3$), 189 ($M^+-H_2O-CH_3CO$); λ_{max} 235 nm; ν_{max} (CCl_4) 3400, 3060, 1700, 1685, 1614 cm^{-1}; δ(CCl_4) 1.00 (6H, s), 1.00–1.20 (4H, m), 1.18 (3H, s), 1.77 (3H, s), 2.48 (2H, s), 2.68 (1H, d, J = 14), 2.84 (1H, d, J = 14), 3.7 (1H, br., OH), 5.68 (1H, s).

[*E*]-*Hypacrone* (**14**). **13** (1.05 g) was pyrolysed by injecting into a GLC column (1.5% SE-30, 1.5 m) kept at 190° (He carrier gas). A liquid (910 mg) was condensed in a cooled trap connected to the outlet of the column. Purification of the condensate by preparative TLC gave 537 mg (55%) of **14** as a colorless liquid; MS (70 eV) *m/e* 232 (M^+), 217 (M^+-CH_3), 214 ($M^+-C_2H_4$), 189 (M^+-CH_3CO), λ_{max} 284 nm (log ϵ: 4.18); ν_{max} (CCl_4) 1700, 1630, 1590 cm^{-1}, δ(CCl_4) 0.92 (2H, m), 1.08 (6H, s), 1.32 (2H, m), 2.08 (6H, s), 2.56 (2H, d, J = 1.5 Hz), 5.88 (1H, br. s), 6.16 (1H, br. s).

[*Z*]-*Hypacrone* (**1**)

Photochemical isomerization of [*E*]-*hypacrone* (**14**). A soln of 65 mg of [E]-hypacrone and 5 mg of 2-acetonaphthone in 0.7 ml of methanol-d_4, placed in a NMR tube, was irradiated at 0° by 450W-Ushio high pressure mercury lamp with a Pyrex filter. The transformation was traced by monitoring the PMR signals at 2.56 ppm ([E]-isomer) and 2.49 ppm ([Z]-isomer) for H-3, or at 5.88 ppm ([E]-isomer) and 5.78 ppm ([Z]-isomer) for H-5 in every 15 min. After 2 hr, [E]-hypacrone was equilibrated with the [Z]-isomer in a ratio of [E]:[Z] = 54:46, which did not change by prolonged irradiation. From the pale yellow equilibrium mixture, the sensitizer and other colored impurities were removed by preparative TLC. A colorless liquid (51 mg; [Z]-[E] mixture) was chromatographed on a fine and long column of neutral alumina (2 mm in dia., 600 mm in length, 4.0 g of Woelm neutral alumina, activity grade II) with hexane:ether (3:1). The fractions were collected in each 1.5 ml portion. The material was eluted from the 28th fraction with the same solvent system. The first 3 fractions contained pure [Z]-hypacrone (combined yield: 4 mg, 6.2%), which crystallized on standing at 0°, m.p. 48–52°. This product was identical with natural hypacrone in IR and PMN spectra. The following fractions were contaminated with increasing amounts of the [E]-isomer, which was combined to recover 34 mg of the mixture. This could be submitted to the photoequilibrium reaction, repeatedly. After complete elution of the isomeric hypacrones with hexane:ether (3:1), the column was washed with ether to afford *ca.* 4 mg of colorless crystals, which was identified with pterosin-Z by IR. Separation of the [Z]- and [E]-isomers of hypacrone was not successful by other conventional separation methods.

Lithium aluminum hydride reduction of [E]*-hypacrone.* An ether soln of [E]-hypacrone (41 mg) was added dropwise with vigorous stirring to a suspension of powdered LAH (30 mg) in anhyd ether. After refluxing for 2 hr, the mixture was worked up as usual. The product, an oily diol (**15**) in quantitative yield, was so unstable, particularly in $CHCl_3$ or CCl_4 soln, that a good PMR spectrum could not be obtained, λ_{max} 249 nm; ν_{max} (neat) 3340, 3080 cm^{-1}, $\delta(CD_3OD)$ 0.4–0.65 (4H, m), 1.00 (3H, s), 1.02 (3H, s), 1.10 (3H, d, J = 6 Hz), 1.91 (3H, s), 2.24 (1H, br), 2.34 (1H, br), 3.40 (1H, q, J = 6 Hz), 4.10 (1H, br), 5.44 (1H, br), 5.82 (1H, br). The diacetate (prepared by Ac_2O-pyridine method); ν_{max} (neat) 3080, 1730, 1378, 1240 cm^{-1}; $\delta(CCl_4)$ 0.5–0.7 (4H, m), 1.00 (3H, s), 1.12 (3H, s), 1.17 (3H, d, J = 6 Hz), 1.90 (3H, d, J = 1.5 Hz), 1.92 (3H, s), 1.95 (3H, s), 2.0–2.4 (2H, m), 4.50 (1H, q, J = 6 Hz), 5.10 (1H, br), 5.40 (1H, br), 5.76 (1H, br).

Photochemical transformation of the diol (**15**).[5] A soln of the diol (5 mg), freshly prepared, in 0.3 ml MeOH was irradiated by Ushio 450W high pressure mercury lamp at 0° in the presence of 1 mg 2-acetonaphthone as sensitizer. The reaction was followed by TLC analysis. The starting material disappeared in *ca.* 15 min. MeOH was evaporated and the residue was purified by preparative TLC. A colorless liquid [3 mg, MS (70 eV) *m/e* 218 (M$^+$), ν_{max} (CCl_4) 3080, 1110 cm^{-1}] was characterized by NMR spectrum in benzene-d_6 as a mixture of epimeric spiroethers, (**17a** and **17b**). **17a**: $\delta(C_6D_6)$ 0.86 (3H, d, J = 6 Hz), 1.05 (3H, s), 1.16 (3H, s), 1.32 (3H, d, J = 1.5 Hz), 1.72 (1H, d, J = 14 Hz), 1.90 (1H, d, J = 14 Hz), 3.92 (1H, q, J = 6 Hz), 5.33 (1H, br s), 5.41 (1H, d, J = 5.5 Hz), 5.59 (1H, d, J = 5.5 Hz). **17b**: $\delta(C_6D_6)$ 0.88 (3H, d, J = 6 Hz), 1.05 (3H, s), 1.16 (3H, s), 1.32 (3H, d, J = 1.5 Hz), 1.80 (1H, d, J = 14 Hz), 1.99 (1H, d, J = 14 Hz), 3.92 (1H, q, J = 6 Hz), 5.33 (1H, br s), 5.52 (1H, d, J = 5.5 Hz), 5.66 (1H, d, J = 5.5 Hz).

Preparation of 5,5-dimethyl-3-iodomethylcyclopentane-1,2-diol acetonide (4)

4,4-Dimethylcyclopentenone (**20**). 3,3-Dimethylglutaroin (120 g, 1 mole), prepared[8] from dimethyl 3,3-dimethylglutarate, was treated with 260 g (1.3 mole) tosyl chloride in 600 ml pyridine for 20 min at −10°. After stirring at room temp. for 10 hr, the mixture was worked up as usual to give a crystalline tosylate, 168 g, m.p. 66–67° (Found: C, 59.55; H, 6.54. Calc. for $C_{14}H_{18}O_4S$: C, 59.61; H, 6.54%); ν_{max} (Nujol) 1755, 1595, 1495, 1370, 1190 cm^{-1}.

The tosylate (60 g) was refluxed with 30 g LiCl in dry acetone (400 ml) for 8 hr. After working up as usual, a mixture (GLC) of 2-chloro-4,4-dimethylcyclopentanone and **20** was obtained. This ketone mixture (95 g) was heated with 70 g LiBr and 70 g Li_2CO_3 in 400 ml DMF for 6 hr at 140°. After cooling, the mixture was diluted with water and extracted with n-pentane. Usual work up of the pentane soln gave **20**, 63 g (88% over all yield from dimethylglutaroin), b.p. 86–87°/63 mm; ν_{max} (neat) 3080, 1710, 1590 cm^{-1}; $\delta(CCl_4)$ 1.24 (6H, s), 2.10 (2H, s), 5.84 (1H, d, J = 6 Hz), 7.31 (1H, d, J = 6 Hz).

3-Acetoxy-5,5-dimethylcyclopentane-1,2-diol (**21**). To a suspension of 25 g of powdered LAH in 500 ml ether was added dropwise a soln of 50 g of **20** in 200 ml ether. After refluxing for 4 hr, the mixture was decomposed with water at 0° and then worked up as usual to give a colorless liquid, 48 g (94%); ν_{max} (neat) 3350, 3040 cm^{-1}. Acetylation of the reduction product (40 g) with 160 ml Ac_2O and 16 g NaOAc (100°, 30 min) gave an acetate, a colorless liquid, 36 g (65%); ν_{max} (neat) 3080, 1730 cm^{-1}. An EtOH (50 ml) soln of the acetate (9.26 g, 60 mmole) was treated at −15° with a $KMnO_4$ soln, prepared from 9.35 g (61 mmole) of $KMnO_4$, 7.2 g (61 mmole) $MgSO_4$ and 200 ml aqueous EtOH (1:1). After stirring for 30 min at −10°, the mixture was diluted with 500 ml water and extracted thoroughly with ether. The diol (**21**), thus obtained, was crystallized from hexane–ether, 8.1 g (72%), m.p. 77–78°. ν_{max} ($CHCl_3$) 3400, 1720 cm^{-1}, $\delta(CDCl_3)$ 1.03 (3H, s), 1.05 (3H, s), 2.08 (3H, s), 1.50 (1H, dd, J = 14, 5 Hz), 2.16 (1H, dd, J = 14, 9 Hz), 2.50 (2H, br, OH), 3.60 (1H, d, J = 5 Hz), 4.10 (1H, t, J = 5 Hz), 4.80 (1H, m). (Found: C, 57.47; H, 8.59. Calc. for $C_9H_{16}O_4$: C, 57.43; H, 8.57%).

Acetonide (**22**) *of 2,3-dihydroxy-4,4-dimethylcylcopentanone.* **21**, (8.1 g) was dissolved in 100 ml dry acetone and treated with 15 g anhyd $CuSO_4$ and 10 mg *p*-toluenesulfonic acid with stirring overnight at room temp. After filtration, the solvent was evaporated. The residue was worked up to give an oily acetonide, 8.5 g (87%), ν_{max} (neat) 1730 cm^{-1}; $\delta(CCl_4)$ 1.00 (3H, s), 1.01 (3H, s), 1.20 (3H, s), 1.36 (3H, s), 1.94 (3H, s), 4.04 (1H, d, J = 6 Hz), 4.43 (1H, t, J = 6 Hz), 4.80 (1H, m). This product was directly hydrolyzed with 1.7 g NaOH in 100 ml MeOH at room temp. for 2 hr. After neutralization with 1 ml AcOH, MeOH was evaporated *in vacuo*. The residue was worked up as usual to leave the hydroxy-acetonide as a colorless liquid, 7.43 g (quantitative), ν_{max} (neat) 3400 cm^{-1}. This (8.2 g, 0.045 mole) was oxidized with ice cooled Collins' reagent,[12] prepared from 27 g (0.27 mole) CrO_3 and 42 g pyridine in methylene chloride. After stirring for 30 min at room temp., the mixture was worked up. The ketone (**22**) was obtained as crystals from hexane–ether, 7.2 g (89%), m.p. 71–72° (Found: C, 65.20; H, 8.78. Calc. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75%). ν_{max} (CCl_4) 1750 cm^{-1}; $\delta(CCl_4)$ 0.95, 1.20, 1.30, 1.37 (each 3H, s), 1.92 (1H, d, J = 17 Hz), 2.42 (1H, d, J = 17 Hz), 4.05 (1H, d, J = 5 Hz), 4.18 (1H, d, J = 5 Hz).

5,5-Dimethyl-3-tosyloxymethylcyclopentane-1,2-diol acetonide (**23**). To a soln of methylene triphenylphosphorane, prepared from methyl triphenylphosphonium bromide (26 g, 0.07 mole) and n-BuLi soln (1.5M in hexane, 42 ml), in THF was added a soln of **22**, 10.4 g (0.057 mole), in THF at room temp. under Argon atmosphere. After stirring overnight at room temp. the mixture was worked up. An exo-methylene olefin, 7.5 g (73%), b.p. 65–75°/18 mm, ν_{max} (neat) 3080 cm^{-1}; $\delta(CCl_4)$ 0.80, 1.04, 1.20, 1.33 (each 3H, s), 1.76 (1H, d, J = 15 Hz), 2.40 (1H, d, J = 15 Hz), 3.92 (1H, d, J = 5 Hz), 4.56 (1H, d, J = 5 Hz), 4.93 (1H, m), 5.02 (1H, m), was directly submitted to hydroboration was follows.

To a soln of 50.5 g (0.6 mole) 2,3-dimethyl-2-butene in 40 ml THF, 26 ml of diborane soln (2.1M in THF) was added at 0° during 10 min under an argon stream, and the mixture was stirred at 0° for 1 hr.[14] A soln of the olefin (7.8 g, 43 mmole) in THF was added to the thexylborane soln at 0°. After standing overnight at room temp. the mixture was decomposed with water, and then treated with alkaline H_2O_2 (30 ml of 3N-NaOH, 30 ml of 30%-H_2O_2, 50°, 2 hr). Usual working up gave a carbinol as a colorless liquid, 8.5 g (quantitative), ν_{max} (neat) 3400 cm^{-1}; $\delta(CDCl_3)$ 0.86, 1.00, 1.20, 1.36 (each 3H, s), 1.20 (1H, d, J = 12 Hz), 1.54 (1H, d, J = 12 Hz), 1.84 (1H, br, OH), 2.10 (1H, m), 3.53 (1H, s), 3.58 (1H, s), 3.94 (1H, d, J = 6 Hz), 4.58 (1H, t, J = 6 Hz), which was treated directly with tosyl chloride (1.07 eq) in pyridine to give a crystalline tosylate (23) in 92% yield, m.p. 97–98° from pentane (Found: C, 61.03; H, 7.42. Calc. for $C_{18}H_{26}O_5S$: C, 61.02; H, 7.38%); ν_{max} ($CHCl_3$) 1600, 1390, 1380, 1185 cm^{-1}.

5,5-Dimethyl-3-iodomethylcyclopentane-1,2-diol acetonide (**4**). **23** (6.5 g, 0.018 mole) was refluxed in 100 ml dry acetone with 6 g (0.04 mole) of NaI. After 20 hr, the mixture was diluted with n-pentane and filtered from the inorganic material. Evaporation of the solvent gave a colorless liquid, which was purified by silicagel column chromatography. The iodomethyl derivative (4), (4.97 g, 88%), ν_{max} (neat) 2920, 1470, 1380 cm^{-1}; $\delta(CCl_4)$ 0.90, 1.00, 1.25, 1.38 (each 3H, s), 1.40 (1H, d, J = 12 Hz), 1.50 (1H, dd, J = 12, 3 Hz), 2.30 (1H, m), 3.10 (1H, dd, J = 12, 10 Hz), 3.20 (1H, dd, J = 12, 10 Hz), 4.04 (1H, d, J = 5 Hz), 4.50 (1H, t, J = 5 Hz).

Preparation of 2,2 - *dimethyl* - 4 - *iodomethylcyclopentanol tetrahydropyranyl ether* (5)

2,2 - *Dimethylcyclopentanone* - 4 - *carboxylic acid* (25). Friedel–Crafts' cyclization of 2,2 - dimethylpent - 4 - enoic acid[7] by Agosta and Smith's procedure[6] gave in *ca.* 60% yield a mixture of two products, 24 and 4 - chloro - 2,2 - dimethylcyclopentanone in 4:3 ratio (by GLC). This mixture (6.8 g) was stirred with 10 g KCN in 200 ml DMSO at 35° for 15 hr. After dilution with water, the mixture was extracted with ether to give a yellow syrup (6.9 g, ν_{max} 2260, 1740 cm^{-1}), which was hydrolyzed by refluxing with dil H_2SO_4 (80 ml water and 30 ml conc. H_2SO_4) for 15 hr. When cooling, 25 separated as crystals, 4.03 g, m.p. 96–98°, ν_{max} ($CHCl_3$) 3400–2600, 1730, 1700 cm^{-1}; $\delta(CDCl_3)$ 0.98 (3H, s), 1.18 (3H, s), 2.0–2.95 (5H, m), 10.8 (1H, OH).

2,2 - *Dimethyl* - 4 - *tosyloxymethylcyclopentanone* (26). A soln of 25 (1.71 g) in 8 ml ether was added dropwise to a suspension of 1.1 g of pwodered LAH in 15 ml ether under refluxing for 3 hr. After working up, a diol was obtained as a colorless liquid (quantitative), which was homogeneous on TLC and GLC, ν_{max} (neat) 3300 cm^{-1}. The diol (1.41 g) was tosylated with 1.91 g (1.02 eq) tosyl chloride in pyridine (0°, 3 hr), to give a monotosylate (syrup, 2.3 g, 80%), ν_{max} (neat) 3300, 1610, 1510, 1190, 1180 cm^{-1}; $\delta(CCl_4)$ 0.65, 0.92, 2.40 (each 3H, s), 4.80 (1H, OH), 7.25 and 7.60 (4H, A_2B_2). The crude tosylate (2.2 g) was treated with Collins' reagent[12] (CrO_3 5.1 g, pyridine 8 g) in methylene chloride at room temp. After 30 min, the mixture was diluted with ether, and filtered from inorganic materials. The organic layer was worked up as usual to give 26 (2.03 g; 93%), which crystallized from hexane–ether; m.p. 83–85°, ν_{max} ($CHCl_3$) 1730, 1600, 1350, 1185 cm^{-1}; $\delta(CDCl_3)$ 0.82, 1.05, 2.45 (each 3H, s), 1.5 (1H, m), 2.0–2.4 (4H, m), 4.10 (2H, m), 7.36 and 7.80 (4H, A_2B_2, J = 8 Hz).

2,2-*Dimethyl*-4-*iodomethylcyclopentanone* (27). 26 (2.01 g) dissolved in 30 ml dry acetone was treated with 3.1 g NaI under reflux for 20 hr. Ether was added and the precipitated inorganic materials removed by filtration. After evaporation *in vacuo*, the residue was purified by preparative TLC giving 27 (1.52 g; 89%) ν_{max} (neat) 1735 cm^{-1}; $\delta(CCl_4)$ 0.85, 1.11 (each 3H, s), 1.5–2.5 (5H, m), 2.8–3.6 (2H, m).

Tetrahydropyranyl ether (5). 27 (1.52 g) in THF was reduced with 18 ml diborane soln (1.5M in THF) at 0° for 10 min. After addition of water, THF was evaporated *in vacuo*. The product was taken up in ether. 2,2 - Dimethyl - 4 - iodomethylcyclopentanol, 1.48 g (97%): ν_{max} (CCl_4) 3300 cm^{-1}. This carbinol (1.3 g) was dissolved in 10 ml anhyd. ether, and treated with 2.5 ml dihydropyrane and 10 mg *p*-toluenesulfonic acid (0°, 1 hr). After working up, the product was purified by preparative TLC, giving 5 (1.43 g; 86%).

Condensation of 4 *and* 5 *with the half-ketal* (3)

Reaction of 4 *with* 3. To a mixture of finely chipped Li metal (210 mg, 30 mg atom) in 4 ml THF was added dropwise a THF soln of 1.04 g (3.4 mmole) of 4 and 690 mg (4.1 mole) of 3 under argon. The mixture was stirred vigorously for 5 hr at room temp. After filtration (to remove some unreacted Li), the soln was poured into water and extracted with ether to give a syrup, which was partially hydrolyzed by stirring with 3 ml 1N HCl in THF at room temp. for 2 hr. After neutralization ($NaHCO_3$), THF was evaporated *in vacuo*. An oily mixture (1.2 g) obtained by extraction with ether was purified by SiO_2 chromatography to afford 670 mg (64.5% from the iodo-compound) of 6 as a colorless liquid, ν_{max} (CCl_4) 3500, 3080, 1690 cm^{-1}; $\delta(CCl_4)$ 0.85, 1.20 (each 2H, m), 0.96, 1.26, 1.40, 1.75, 2.12 (each 3H, s), 3.00 (1H, br, OH), 3.90 (1H, d, J = 8 Hz), 4.50 (1H, t, J = 8 Hz).

Pyrolytic dehydration of the ketol (6). An ether soln of 6, 150 mg, was injected into a GLC column (5%-Apiezon L, 1.5 m, He carrier gas) kept at 240°. A liquid material, which condensed in a cooled trap connected to an outlet of the column, was fractionated by preparative TLC to give two dehydration products, 7 (48 mg, 35%) and 8 (33 mg, 24%). The spectral data of both olefins were as follows; 7: MS (70 eV) 292 (M^+), ν_{max} (neat) 3080, 1695, 880 cm^{-1}; $\delta(CCl_4)$ 0.92, 1.00, 1.20, 1.36, 2.08 (each 3H, s), 1.75 (3H, d, J = 2 Hz), 0.8, 1.2 (each 2H, m), 2.70 (1H, m), 3.93 (1H, d, J = 7 Hz), 4.46 (1H, t, J = 7 Hz), 5.50 (1H, dd, J = 10, 2 Hz); 8: MS (70 eV) 292 (M^+), ν_{max} (neat) 3080, 1695, 1645, 880 cm^{-1}; $\delta(CCl_4)$ 0.90, 0.98, 1.20, 1.34 2.10 (each 3H, s), 0.94, 1.20 (each 2H, m), 3.90 (1H, d, J = 9 Hz), 4.50 (1H, t, J = 9 Hz), 5.00 (2H, s).

Hydrolysis of 7. 7 (162 mg) was refluxed with 4 ml 60%-AcOH for 1 hr. The mixture was worked up to give 7a, 135 mg (96%), which was purified by TLC, ν_{max} ($CHCl_3$) 3300, 3080, 1680 cm^{-1}; $\delta(CDCl_3)$ 1.00, 1.07, 2.06 (each 3H, s), 1.00, 1.20 (each 2H, m), 1.74 (3H, d, J = 2 Hz), 2.60 (2H, OH), 3.00 (1H, m), 3.60 (1H, d, J = 4 Hz), 4.20 (1H, dd, J = 7, 4 Hz), 5.40 (1H, m).

Monotosylate (7b) *of the diol* (7a). 7a (48 mg) was treated with 55 mg (1.1 eq) tosyl chloride in pyridine at −20°. The mixture was kept at room temp. for 3 hr. A colorless syrup (36 mg, 47%), obtained by usual working up, was purified by TLC, ν_{max} ($CHCl_3$) 3600, 1690, 1610, 1500, 1190, 1180 cm^{-1}; $\delta(CDCl_3)$ 0.90, 1.26 (each 2H, m), 0.95, 1.04, 2.10, 2.44 (each 3H, s), 1.70 (3H, d, J = 2 Hz), 2.16 (1H, OH), 2.80 (1H, m), 4.17 (1H, dd, J = 6, 4 Hz), 4.38 (1H, d, J = 4 Hz), 5.52 (1H, m), 7.34, 7.80 (each 2H, d, J = 9 Hz).

Reaction of 5 *and* 3. 5 (900 mg, 2.66 mmole), was treated with 3 and matallic Li by the same procedure as the reaction of 4 with 3. After hydrolysis with 60%-AcOH, 320 mg (47% from the iodo compound) of 9 was obtained as a colorless liquid, ν_{max} (neat) 3400, 3080, 1670 cm^{-1}; $\delta(CDCl_3)$ 0.63, 0.93, 1.05, 1.83 (each 3H, s), 2.0–2.5 (br, OH). 9 (240 mg) was dissolved in 2 ml acetone, and oxidised with Jones' reagent (1 ml) at room temp. (30 min). The product was purified by preparative TLC, to give 159 mg (67%) of a colorless liquid; ν_{max} (neat) 3500, 3080, 1730, 1675 cm^{-1}; $\delta(CCl_4)$ 0.73, 0.90, 1.16, 1.80 (each 3H, s), 2.80 (1H, OH). Dehydration of this oxidation product was performed by a method analogous to the reaction of 6, by passing through a GLC column kept at 230°. The crude product was a mixture of two olefins, 10 and its double bond isomer in 47:53 ratio, from which 4,5-dihydrohypacrone (10) was separated by preparative TLC, $\delta(CCl_4)$ 0.83, 0.96, 2.08 (each 3H, s), 1.80 (3H, d, J = 2 Hz), 5.40 (1H, br d, J = 10 Hz). The double bond isomer of 10: $\delta(CCl_4)$ 0.80, 1.00, 2.08 (each 3H, s), 5.08 (2H, br s).

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