[Chem. Pharm. Bull. 33(7)2783—2791(1985)]

Synthesis of 8-Hydroxy-6-protoilludene, a Probable Biosynthetic Intermediate of Humulene-Derived Sesquiterpenes Produced by Basidiomycetes

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(Received October 29, 1984)

8-Hydroxy-6-protoilludene (**9**), a probable biosynthetic intermediate of humulene-derived sesquiterpenes, was synthesized. A synthetic intermediate, the 2,9-*cis*-2,3-*anti* enone **15**, was found to be unstable under basic conditions and was readily isomerized to the *trans-anti* isomer **23**.

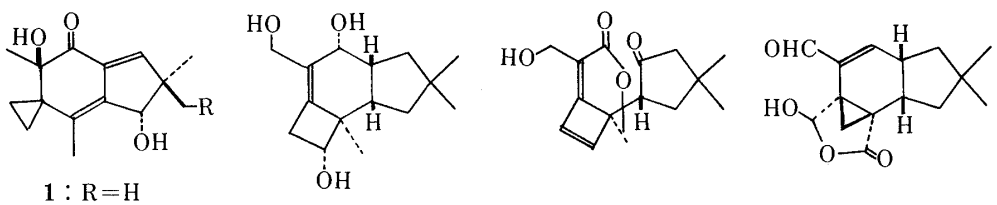
Keywords——humulene-derived sesquiterpene; Basidiomycete; epimerization; 8-hydroxy-6-protoilludene; 6-protoilluden-8-one; 9-*epi*-8-protoilluden-8-one; X-ray analysis

Introduction

Basidiomycetes produce a variety of sesquiterpenes such as illudin-M (**1**),[1a-c] illudin-S (**2**),[1] illudol (**3**),[1a,2] fomannosin (**4**)[3] marasmic acid (**5**)[4] and so on (Fig. 1). These compounds[5] have been postulated to be biosynthesized through humulene (**6**) as illustrated in Chart 1. The hydrocarbon **8**, which may be formed from the protoilludane C-7 cation (**7**) by deprotonation, might be oxidized to the corresponding allylic alcohol **9** or its equivalent **10**, which would rearrange to a cyclobutyl cation (**11**) with the protoilludane skeleton. Through this carbonium cation, illudane (**12**), illudalane (**13**) and marasmane (**14**) type carbon skeletons may be formed by solvolytic processes. As a result of attempts to isolate biosynthetic precursors such as **8**, **9** or **10**, we isolated 6-protoilludene (**8**) and 6-hydroxy-7-protilludene (**10**) from *Fomitopsis insularis* and/or *Omphalotus olearius*.[6] The presence of these compounds in illudin-producing fungi prompted us to attempt the synthesis of isotope-labeled **8** for a feeding experiment as well as the syntheses of the allylic alcohols **9** and **10** to investigate whether their solvolytic behavior simulates the biological cyclobutyl cation rearrangement.[7,8] In this report, we describe a synthesis of the allyl alcohol **9** (Chart 2).

Synthesis

All the naturally occurring protoilludane derivatives including illudol **3**, **8** and **10** possess



1 : R=H
2 : R=OH

3 4 5

Fig. 1

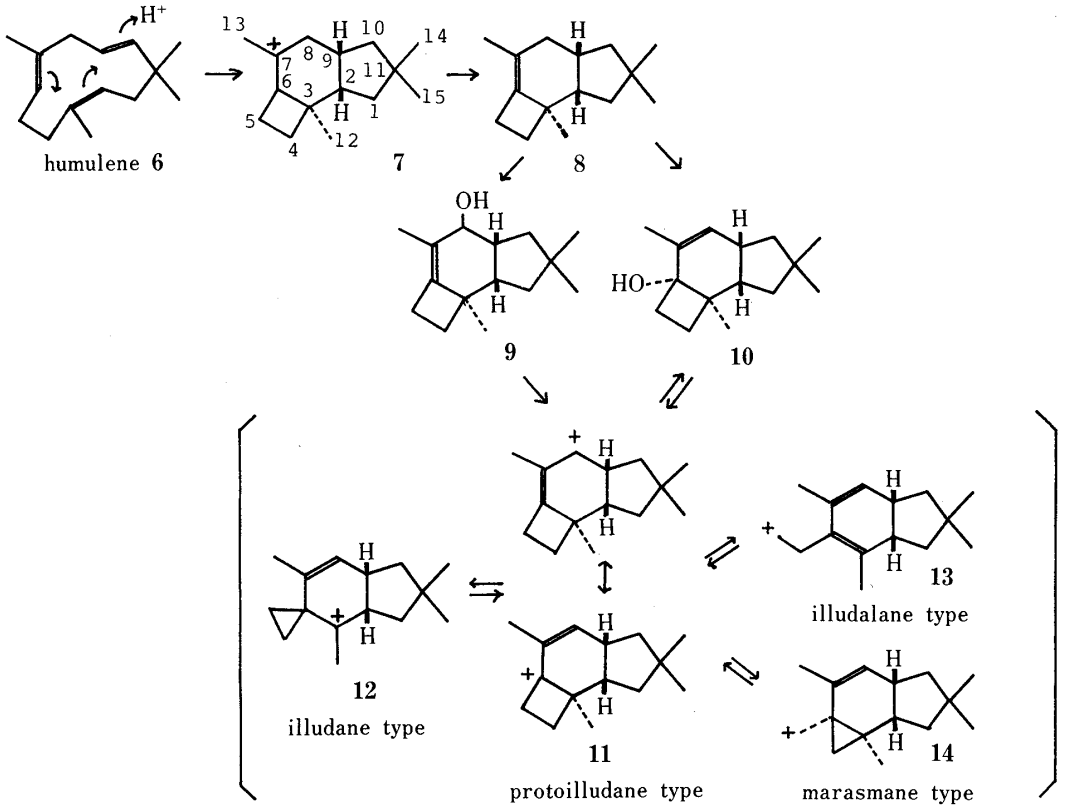


Chart 1

a 2,9-*cis*-2,3-*anti* 5/6/4-fused ring system. Compound **15** with this skeleton was constructed through a route reported by Matsumoto *et al.*[9]

The enol acetate (**16**)[9] was quantitatively converted to **18** by [2+2]photo-cycloaddition with ethylene. Addition of the olefin occurred from the less hindered side of **16**.[10] The keto-acetate **18** was added to excess EtLi to give the diols **19** and **20** in 78% and 8% yields, respectively. The diol **19** was readily oxidized with $NaIO_4$ to the dione **21** (98%) while the diol **20** was unaffected under the same reaction conditions, indicating that the diol in **19** was in *cis* configuration. It seems noteworthy that the *trans* diol **20** was the exclusive product when the keto-acetate **18** was treated with EtMgBr in place of EtLi.

The aldol condensation of the dione **21** on treatment with 5% KOH–MeOH at room temperature gave a mixture of a hydroxy-ketone (**22**) and an enone (**23**). The hydroxy-ketone **22** was converted to **23** upon heating the reaction mixture to reflux.

The structure of **23** was determined by X-ray crystallographic analysis. As shown in Fig. 2, which illustrates an ORTEP drawing[11] of the molecule, the enone **23** was proved not to be the desired 2,9-*cis*-2,3-*anti* structure **15** but to be the epimerized *trans-anti* structure. The atomic coordinates and isotropic temperature factors are listed in Table I. Bond lengths and bond angles are shown in Fig. 3 and selected torsion angles are listed in Table II. More details of the analysis are presented in the experimental section.

In order to avoid the epimerization at C-9 during the aldol condensation, the dione **21** was treated with piperidine in ether to give the desired hydroxy-ketone **17**[12] in 84% yield. On prolonged treatment under aldol reaction conditions, **22** was again formed from **17**. The stereochemistry at C-2, C-3 and C-9 of **17** was confirmed at the stage of **27** by comparison with an authentic specimen prepared from the hydrocarbon **28**.

Dehydration of the hydroxy-ketone **17** to the *cis-anti* enone **15** was attempted under various conditions, *e.g.*, MsCl, MsCl–SO_2, $POCl_3$, $SOCl_2$, dicyclohexylcarbodiimide (DCC),

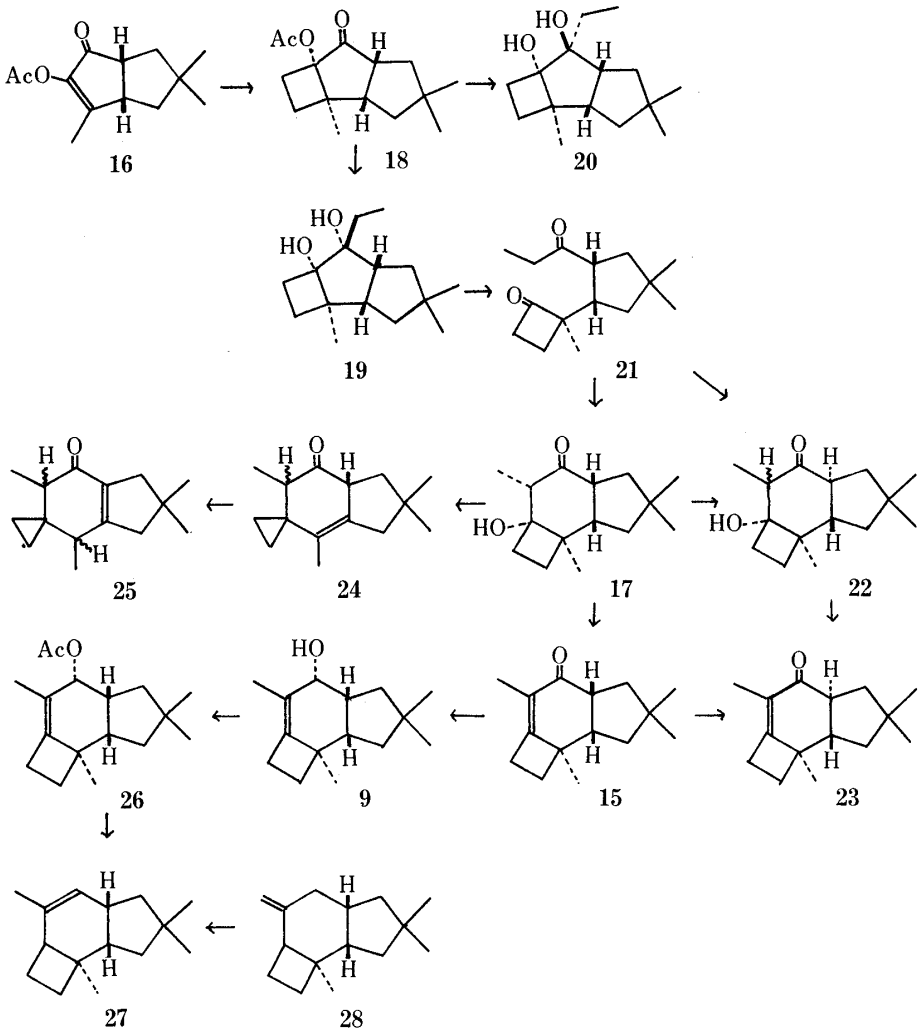


Chart 2

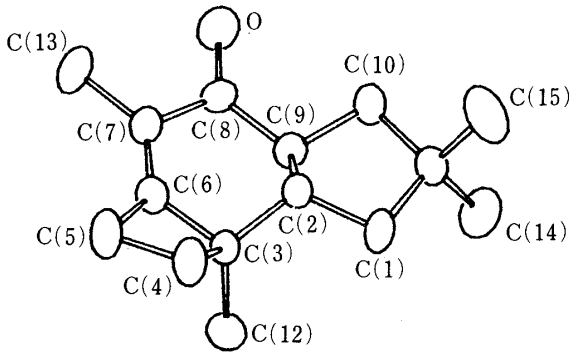


Fig. 2. An ORTEP Drawing of the Molecule of **23** along with Atomic Numbering

Thermal ellipsoids are depicted at the 50% probability level. Hydrogen atoms are omitted for clarity.

dimethylsulfoxide (DMSO), heramethylphosphoric triamide (HMPA), I_2, Al_2O_3 and Florisil, but the yield of the enone **15** was poor in every case. For instance, refluxing of **17** for 1 h with Florisil in benzene or heating at 80 °C for 1 h with alumina (Woelm, activity I) in pyridine readily induced *cis* (**17**) to *trans* (**22**) isomerization. With other dehydrating reagents, either the starting material **17** was recovered or products including the enone **23** and/or a rearranged product **24** were formed. The best method so far found to obtain the enone **15** (24% yield) from **17** was treatment of **17** with MsCl (5 eq) in pyridine at 105—110 °C for 8—10 min. Although the enone **15** was stable in boiling pyridine without MsCl for 20 min, it was

TABLE I. Atomic Coordinates (fractional $\times 10^4$, for H $\times 10^3$) and Isotropic Thermal Parameters (A^2) with Estimated Standard Deviations in Parentheses

No.	Atom	X	Y	Z	B_{eq}
1	C(1)	4831 (2)	2948 (3)	−3863 (3)	3.98 (0.04)
2	C(2)	5099 (2)	3103 (3)	−2159 (3)	3.29 (0.03)
3	C(3)	6063 (2)	3073 (3)	−1230 (3)	3.18 (0.03)
4	C(4)	6612 (2)	4491 (3)	−775 (3)	3.30 (0.04)
5	C(5)	6875 (2)	3972 (4)	878 (3)	3.27 (0.05)
6	C(6)	6101 (2)	2943 (3)	392 (3)	3.53 (0.04)
7	C(7)	5489 (2)	2504 (3)	991 (3)	4.63 (0.04)
8	C(8)	4665 (2)	1904 (3)	−50 (3)	5.02 (0.04)
9	C(9)	4624 (2)	1848 (3)	−1672 (3)	3.31 (0.04)
10	C(10)	3715 (2)	1902 (4)	−2817 (3)	3.81 (0.05)
11	C(11)	3872 (2)	2373 (3)	−4300 (3)	3.31 (0.04)
12	C(12)	6607 (2)	1919 (4)	−1716 (4)	5.61 (0.05)
13	C(13)	5539 (2)	2619 (4)	2615 (3)	6.06 (0.05)
14	C(14)	3773 (2)	1104 (4)	−5384 (4)	4.44 (0.06)
15	C(15)	3226 (3)	3563 (5)	−5042 (5)	9.18 (0.08)
16	O	4055 (1)	1542 (3)	406 (2)	6.51 (0.04)
17	HC1	523 (2)	223 (4)	−426 (4)	7 (1)
18	HC1′	494 (3)	371 (6)	−453 (5)	10 (1)
19	HC2	484 (2)	399 (3)	−192 (3)	4 (1)
20	HC4	711 (2)	477 (4)	−127 (3)	5 (1)
21	HC4′	623 (2)	542 (4)	−90 (3)	5 (1)
22	HC5	685 (2)	468 (4)	172 (4)	6 (1)
23	HC5′	751 (2)	340 (4)	110 (4)	6 (1)
24	HC9	495 (2)	91 (3)	−181 (3)	4 (1)
25	HC10	330 (3)	244 (5)	−240 (5)	8 (1)
26	HC10′	342 (3)	88 (5)	−300 (5)	9 (1)
27	HC12	672 (2)	216 (4)	−285 (4)	6 (1)
28	HC12′	721 (2)	189 (4)	−103 (4)	5 (1)
29	HC12″	633 (3)	93 (4)	−176 (4)	8 (1)
30	HC13	498 (2)	310 (4)	281 (4)	6 (1)
31	HC13′	537 (3)	168 (5)	305 (5)	10 (1)
32	HC13″	602 (4)	312 (7)	320 (7)	14 (2)
33	HC14	389 (2)	131 (4)	−644 (4)	6 (1)
34	HC14′	423 (3)	33 (5)	−481 (4)	9 (1)
35	HC14″	312 (3)	74 (4)	−561 (4)	7 (1)
36	HC15	262 (3)	327 (5)	−517 (5)	9 (1)
37	HC15′	337 (3)	379 (5)	−609 (5)	8 (1)
38	HC15″	334 (4)	455 (6)	−441 (6)	13 (2)

For non-hydrogen atoms: $B_{eq}=\frac{4}{3}\sum_i\sum_j(\boldsymbol{a}_i\cdot\boldsymbol{a}_j)\cdot\beta_{ij}$.

gradually epimerized to **23** under the reaction conditions.[13] Therefore, the product enone **15** was always accompanied by the enone **23**. When MsCl was added in a smaller amount (*i.e.*, 2 eq), a part of the hydroxy-ketone **17** epimerized to **22**, and a larger amount of MsCl (*i.e.*, 10 eq) accelerated the epimerization of **15** to its epimeric enone **23**. The enone **15**, thus obtained, spontaneously isomerized to **23** on contact with a 5% KOH–MeOH solution. Proton and carbon-13 nuclear magnetic resonance (^{1}H- and ^{13}C-NMR) data for **15** and **23** are summarized in Tables III and IV and Fig. 4.

When the dehydration with MsCl in pyridine was carried out at lower temperature (at 0 °C or room temperature), the major product was a ketone **24** with an illudane skeleton; this

TABLE II. Selected Torsion Angles (°) with Estimated Standard Deviations in Parentheses

O	– C(8)	– C(7)	– C(6)	–176.4 (2)	C(7)	– C(6)	– C(3)	– C(2)	19.2 (3)
C(9)	– C(8)	– C(7)	– C(6)	0.7 (3)	C(13)	– C(7)	– C(6)	– C(5)	–18.6 (4)
C(8)	– C(7)	– C(6)	– C(5)	158.5 (1)	C(13)	– C(7)	– C(6)	– C(3)	–170.3 (1)
C(8)	– C(7)	– C(6)	– C(3)	6.8 (3)	C(6)	– C(3)	– C(2)	– C(9)	–49.7 (2)
C(7)	– C(6)	– C(5)	– C(4)	–139.6 (3)	C(3)	– C(2)	– C(9)	– C(8)	59.6 (2)
C(7)	– C(6)	– C(3)	– C(4)	141.5 (2)	C(2)	– C(9)	– C(8)	– C(7)	–34.2 (3)
C(6)	– C(5)	– C(4)	– C(3)	–18.1 (2)	C(1)	– C(2)	– C(9)	– C(10)	–43.1 (2)
C(3)	– C(6)	– C(5)	– C(4)	18.9 (2)	C(4)	– C(3)	– C(2)	– C(1)	94.1 (2)
C(5)	– C(4)	– C(3)	– C(6)	18.3 (2)	C(12)	– C(3)	– C(2)	– C(9)	76.4 (2)
C(4)	– C(3)	– C(6)	– C(5)	–18.7 (2)	C(5)	– C(4)	– C(3)	– C(12)	–94.5 (2)

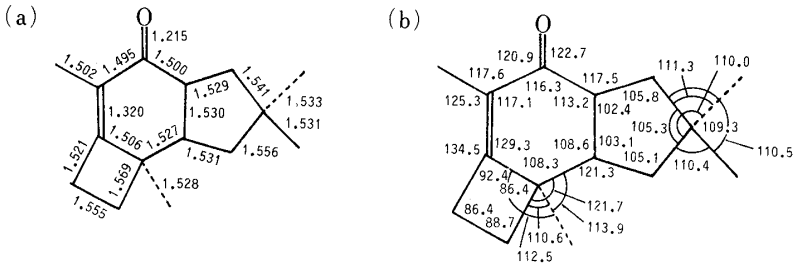


Fig. 3. (a) Bond Length (Å) for Non-hydrogen Atoms
Estimated standard deviations are 0.003—0.005 Å.
(b) Bond Angles (°) for Non-hydrogen Atoms
Estimated Standard deviations are 0.2—0.3°.

TABLE III. ^{1}H-NMR Chemical Shifts δ (ppm) and Coupling Constants J_{HH} (Hz) of the Enones **15** and **23**[a)]

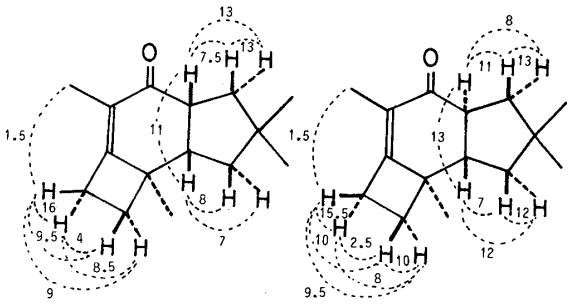
Proton	**15**		**23**	
	δ	J_{HH}	δ	J_{HH}
$H_{1\alpha}$	1.55	7	1.28	12, 12
$H_{1\beta}$	1.55	8	1.42	7, 12
H_2	2.75	7, 8, 11	2.25	7, 12, 13
$H_{4\alpha}$	1.91	8.5, 9	1.81	8, 9.5, 10
$H_{4\beta}$	1.91	4, 9.5	1.91	2.5, 8, 10
$H_{5\alpha}$	2.76	4, 8.5, 16	2.71	2.5, 8, 15.5
$H_{5\beta}$	3.00	1.5, 9, 9.5, 16	2.52	1.5, 9.5, 10, 15.5
H_9	2.96	7.5, 11, 13	2.52	8, 11, 13
$H_{10\alpha}$	1.45	13, 13	1.78	8, 13
$H_{10\beta}$	1.84	7.5, 13	1.47	11, 13
H_{13}	1.64	1.5	1.61	1.5
H_{12}	1.22		1.30	
H_{14}	1.11		1.06	
H_{15}	0.98		1.02	

a) The numbering of carbons is shown in the structure **7** in Chart 1.

was the exclusive product on dehydration of **17** with $SOCl_2$ in pyridine at 0 °C for 10 min. Compound **24** was instantly isomerized to the conjugated ketone **25** in $CHCl_3$ or CCl_4. The structures of **24** and **25** were determined by ^{1}H-NMR and mass spectra (MS) analyses. The ^{1}H-NMR spectrum of **25** showed a multiplet at 0.33—0.48 (4H) due to the methylenes on cyclopropane, and two doublets at 0.92 (3H, J=7.5 Hz) and 1.06 (3H, J=7.5 Hz) due to two methyls on C-3 and C-7.

TABLE IV. ^{13}C-NMR Chemical Shifts δ (ppm) of the Enones **15** and **23**

Carbon	15	23
1	40.2	41.9
2	45.9	55.6
3	45.6	49.0
4	34.7	33.3
5	27.5	30.2
6	167.5	169.4
7	125.8	125.2
8	201.7	201.8
9	51.5	50.0
10	43.4	40.5
11	39.2	36.8
12	23.9	16.3
13	10.0	9.5
14	29.2	31.8
15	29.4	31.8



15 **23**

Fig. 4. ^{1}H-NMR Coupling Constants J_{HH} (Hz) of **15** and **23**

The 2,9-*cis*-2,3-*anti* allyl alcohol **9** was quantitatively obtained by reduction of the enone **15** with lithium aluminum hydride (LAH). The acetate **26** was reduced with Li in $EtNH_2$ to give a hydrocarbon **27** which had spectral (^{1}H-NMR, MS) and chromatographic properties identical with those of 7-protoilludene derived from a synthetic hydrocarbon, **28**.[6,10,14] Thus, the allyl alcohol **9** was determined to have the *cis-anti* ring system, so the enone **15** was also confirmed to have the *cis-anti* ring system. The ^{1}H-NMR spectrum of **9** showed four singlets at 0.93 (3H), 1.03 (3H), 1.08 (3H) and 1.63 (3H) and a broad doublet at 3.97 (1H, J=8 Hz, proton on C-8). The stereochemistry of the hydroxy group of **9** was assigned as α from the coupling constant between the protons on C-8 and C-9.

Discussion

During the synthetic studies on the allyl alcohol **9**, the 2,9-*cis*-2,3-*anti* enone **15** was found to be unstable under basic conditions, being readily isomerized to the *trans-anti* isomer **23**. In the case of bicyclo [4.3.0]nonan-1-ones and bicyclo[4.3.0]non-2-en-1-ones, the *cis* form is more stable than the *trans* form.[15,16] It is noteworthy that, in the case of 6-protoilluden-8-ones, the 2,9-*trans* form as in **23** is more stable than the 2,9-*cis* form as in **15**.[10,17-19] In order to explain the relative stabilities of **15** and **23** together with other related enones, we performed molecular mechanical calculations using the MMPI program developed by Allinger.[20,21] The results will be described in the following paper.

The allyl alcohol **9**, obtained by reduction of the enone **15**, has an attractive structure and an appropriate oxidation level for a role as an intermediate in the biosynthesis of humulene-derived sesquterpenes. In the biosynthesis, the 7-protoilludene C-7 cation (**11**) which may be derived from this allyl alcohol **9** or its isomer **10** would be transformed into illudane, marasmane or illudalane compounds by cyclobutyl cation rearrangement. The solvolytic reactions of the allyl alcohols **9** and **10** will be described elsewhere.

Experimental

^{1}H-NMR spectra were measured on a JEOL GX-400 FT-NMR spectrometer (400 MHz for ^{1}H) and chemical shifts were recorded in δ units relative to internal tetramethylsilane (TMS) (δ=0) in $CDCl_3$. ^{13}C-NMR spectra were measured on the same spectrometer (100 MHz). Infrared (IR) spectra were measured on a JASCO DS-301 or A-102

instrument, ultraviolet (UV) spectra on a Shimadzu UV-300 spectrometer, and MS on a Shimadzu-LKB 9000 machine at 70 eV. Melting points are uncorrected. Elementary analyses were performed by the Microanalytical Laboratory, Institute of Applied Microbiology, the University of Tokyo.

***cis-anti-cis*-3-Acetoxy-6,9,9-trimethyltricyclo[5.3.0.0^{3,6}]decan-2-one (18)**——*cis*-3-Acetoxy-4,7,7-trimethyl-bicyclo[3.3.0]oct-3-en-2-one (**16**)[9] (5.0 g) was dissolved in acetone (150 ml) and ethylene was bubbled through the solution which was irradiated at 0 °C for 10 h with a 450 W high-pressure mercury lamp equipped with Corex filter. The acetone was removed under reduced pressure to give **18** (5.4 g, 98% yield). The oily product was used as such in subsequent experiments. **18**: ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, s, CH_3), 1.10 (6H, s, $CH_3 \times 2$), 2.08 (3H, s, CH_3CO). IR (film) ν: 1748 cm^{-1} (cyclopentanone, acetate), 1250 cm^{-1} (acetate). MS *m/z*: 250 (M^+), 222 ($M^+ - C_2H_4$), 208 (base peak). *Anal.* Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; O, 19.17. Found: C, 71.76; H, 8.74; O, 19.14.

***cis-anti-cis*-2β-Ethyl-6,9,9-trimethyltricyclo[5.3.0.0^{3,6}]decan-2α,3α-diol (19) and *cis-anti-cis*-2α-Ethyl-6,9,9-trimethyltricyclo[5.3.0.0^{3,6}]decan-2β,3α-diol (20)**——The tricyclic keto-acetate **18** (7.75 g, 31 mmol) in anhydrous ether (150 ml) was added dropwise to EtLi (450 ml, 126 mmol) in ether under nitrogen at 0 °C. During the course of the reaction, the amounts of **18**, **19** and **20** were checked by thin-layer chromatography (TLC) (precoated silica gel plate/benzene : acetone = 10 : 1). When the reaction was completed, the reaction mixture was poured into ice-water mixture containing NH_4Cl. The ether layer was separated and the aqueous layer was extracted with ether. The ether solution was washed with brine, and dried over anhydrous Na_2SO_4, then the ether was removed. The residual mixture consisted of **19** (5.7 g, 78% yield) and **20** (0.6 g, 8% yield). When 3 eq of EtMgBr in ether was used instead of EtLi, the *trans* diol **20** was obtained as a major product accompanied by a small amount of the *cis* diol **19**. The diols **19** and **20** were separated by silica gel column chromatography. **19**: ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s, CH_3), 1.01 (3H, s, CH_3), 0.87 (3H, t, J=7.5 Hz, $C\underline{H}_3CH_2$). IR (KBr) ν: 3410 cm^{-1} (OH). MS *m/z*: 238 (M^+), 220 ($M^+ - H_2O$), 205 ($M^+ - H_2O - CH_3$, base peak), 191, 181, 163. *Anal.* Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.36; H, 11.15. **20**: mp 79—80 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (6H, s, $CH_3 \times 2$), 1.03 (3H, t, J=7.5 Hz, $C\underline{H}_3CH_2$), 1.04 (3H, s, CH_3). IR (KBr) ν: 3460 cm^{-1} (OH). MS *m/z*: 238 (M^+), 220 ($M^+ - H_2O$), 205, 191, 181, 163 (base peak). *Anal.* Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.75; H, 10.90.

6,7-Secoprotoilludan-6,8-dione (21)——The diol **19** (14.0 g) was dissolved in MeOH (2.90 l) and the solution was added to a solution of $NaIO_4$ (22 g) in water (2.6 l). The mixture was shaken for 10 d, then extracted with ether. The ether solution was washed with brine and dried over anhydrous Na_2SO_4. After removal of the ether, **21** was obtained (13.6 g, 98% yield). ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.02 (3H, t, J= 7.5 Hz, $C\underline{H}_3CH_2$). IR (film) ν: 1719 cm^{-1} (C=O), 1781 (cyclobutanone). MS *m/z*: 236 (M^+), 221 ($M^+ - CH_3$), 208 ($M^+ - C_2H_2$), 151 (base peak). *Anal.* Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.52; H, 10.20.

9-*epi*-6α-Hydroxyprotoilludan-8-one (22) and 9-*epi*-6-Protoilluden-8-one (23)——The diketone **21** (270 mg) in MeOH (15 ml) was mixed with KOH (10%)–MeOH (2 ml) and the reaction mixture was refluxed for 3 h, concentrated to half the initial volume, and, after addition of water, extracted with ether. The ether solution was washed with brine, then dried over Na_2SO_4 and the ether was removed. The residual oil was chromatographed on silica gel/benzene : acetone = 19 : 1 to give colorless prisms (**23**, 224—237 mg, 90—95% yield). When the reaction was conducted overnight at room temperature, a mixture of **22** and **23** was obtained. Compounds **23** and **22** were separated by silica gel column chromatography. **23**: mp 53—54 °C (ether). For ^{1}H-NMR data, see Table III and Fig. 3. For ^{13}C-NMR data, see Table IV. IR (KBr) ν: 1662 cm^{-1} (enone). UV (EtOH) λ: 249 nm (ε=12700). MS *m/z* (218-100): 218 (M^+, 100%), 203 (86%), 189 (61%), 175 (52%), 161 (40%), 149 (37%), 147 (46%), 133 (33%), 119 (59%), 107 (40%), 105 (56%). *Anal.* Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.72; H, 10.29. **22**: ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, s, CH_3), 1.13 (3H, s, CH_3), 1.25 (3H, s, CH_3), 1.07 (3H, d, J=7.4 Hz, CH_3). IR (film) ν: 1705 cm^{-1} (cyclohexanone). MS *m/z*: 236 (M^+), 208 ($M^+ - C_2H_2$), 123 (base peak).

X-Ray Structure Analysis of 9-*epi*-6-Protoilluden-8-one (23)——Colorless prisms were obtained from hexane solution. Crystal data are: monoclinic $P2_1/a$, a=15.904 (6) Å, b=9.295 (4), c=9.348 (4), β=106.89 (5)°, V=1322 (1) Å^3, z=4, λ(Cu$K\alpha$)=1.5402 Å, μ=1.19 mm^{-1}, D_x=1.10 g·cm^{-3}. Intensity data were measured on a Philips PW100 four-circle diffractometer using monochromated Cu$K\alpha$ radiation. The crystal was very labile and the intensities decreased to about half in a day. Monitoring of three reference reflections every 120 min was carried out throughout the data collection process, and the crystal was replaced with a new one at the stage of 30% deterioration. Three crystals were used for data collection. Reflections within 2θ=140° were measured by the θ–2θ scan method with a scan speed of 6°/min in θ. A total of 2025 non-zero, independent reflections were used for structure determination. Correction for crystal deterioration was made by linearly interpolating the intensities of reference reflections. The structure was solved by the direct method using the MULTAN program[22] and refined by the block-diagonal least-squares method.[23] Hydrogen atoms were generated computationally on the basis of stereochemical and geometrical considerations. The final *R*-factor was 0.085 assuming anisotropic thermal motions for non-hydrogen atoms and isotropic ones for the hydrogen atoms. The unit weight was applied for all reflections. Atomic scattering factors for non-H atoms were taken from International Tables for X-Ray Crystallography (1974)[24] and those for hydrogen atoms were taken from Stewart *et al.*[25]

6α-Hydroxyprotoilludan-8-one (17)——Piperidine (0.9 ml) was added to a solution of **21** (450 mg) in ether (12 ml), and the whole was stirred for 40 h at 28 °C. During the course of the reaction, aliquots were collected and

analyzed by gas chromatography (GC). Relative retention times of **21**, **22** and **17** were 1, 1.36 and 1.41 (OV-1, 0.28 mm i.d., 30 m, 140 °C) and 1, 1.63 and 1.74 (OV-17, 0.28 mm i.d., 30 m, 180 °C), respectively. Longer reaction time decreased the yield of **17** because of the isomerization of **17** to **22**. When the reaction was completed, the ether and piperidine were removed under a vacuum, and the resulting crystalline compound was recrystallized from ether to give 380 mg (84% yield) of the ketol **17**. mp 124—125 °C (ether). ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.07 (3H, d, J=7.4 Hz, CH_3), 1.03 (dd, J=13, 13 Hz, $H_{1\alpha}$), 1.24 (dd, J=8, 13.5 Hz, $H_{10\beta}$), 1.2 (dd, J=6, 13 Hz, $H_{1\beta}$), 2.25 (dd, J=2, 13.5 Hz, $H_{10\alpha}$), 2.59 (ddd, J=6, 8, 13 Hz, $H_{2\beta}$), 2.95 (q, J=7.4 Hz, $H_{7\beta}$), 3.07 (ddd, J=2, 8, 8 Hz, $H_{9\beta}$). IR (KBr) ν: 1708 cm^{-1} (cyclohexanone). MS m/z: 236 (M^+), 208 ($M^+ - C_2H_2$), 123 (base peak).

6-Protoilluden-8-one (15)——The ketol **17** (200 mg) in pyridine (2.5 ml) was heated in an oil bath at 105—110 °C under stirring and then added to a solution of MsCl (0.3 ml, 5 eq) in one portion. After 8—10 min, the flask was dipped into an ice-water bath and 5 ml of cold water was poured into the flask. The resulting mixture was extracted with ether and the ether solution was washed successively with 1 N HCl, saturated $NaHCO_3$ and brine. Removal of the solvent after drying over Na_2SO_4 gave a mixture of the enones **15** and **23**, which were separated by silica gel column chromatography with benzene to give 25 mg of **23** and 45 mg (24% yield) of **15**. The yield of **15** depended on the reaction conditions. ^{1}H- and ^{13}C-NMR data are listed in Tables III, IV and Fig. 3. IR (KBr) ν: 1661 cm^{-1} (enone). UV (EtOH) λ: 250 nm (ε=8580). MS m/z (218-100): 218 (M^+, 100%), 203 (73%), 189 (76%), 175 (38%), 161 (63%), 149 (76%), 147 (36%), 133 (33%), 119 (50%), 107 (40%), 105 (50%).

Epimerization of 15 to 23 with KOH–MeOH——The enone **15** (2 mg) was dissolved in 0.1 ml of KOH (5%)–MeOH and the solution was stirred. From the result of GC analysis of the reaction mixture, it became clear that equilibrium (**15**:**23**=1:45) was attained within a minute at room temperature.

2-Illuden-8-one (24) and 2 (9)-Illuden-8-one (25)——A solution of the ketol **17** (35 mg) in pyridine (1 ml) was treated with $SOCl_2$ (0.2 ml) at 0 °C. The reaction mixture was stirred for 10 min, then cold water was added to it. The products were extracted with ether. The ether layer was washed successively with 1 N HCl, saturated $NaHCO_3$ and brine, and dried over Na_2SO_4 (more than 90% yield by GC). Compound **24** was stable in ether, but unstable in $CHCl_3$ or CCl_4, where it instantly changed to the isomer **25**, which was purified by GC. **24**: MS m/z (218-100): 218 (M^+, 86%), 203 ($M^+ - CH_3$, 36%), 190 ($M^+ - CO$ and/or $M^+ - C_2H_2$, 26%), 189 (14%), 175 (58%), 162 (36%), 161 (28%), 147 (36%), 135 (80%), 134 (80%), 119 (100%), 106 (44%), 105 (78%). **25**: ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=7 Hz, methyl protons on C-13), 1.10 (6H, s, $CH_3 \times 2$), 1.06 (3H, d, J=7.5 Hz, methyl protons on C-12), 1.99 (1H, q, J=7.5 Hz, proton on C-3), 2.37 (2H, methylene protons on C-1), 2.25 (1H, d, J=18 Hz, proton on C-10), 2.42 (1H, d, J=18 Hz, proton on C-10), 2.4 (1H, q, J=7.0 Hz, proton on C-7), 0.33—0.48 (4H, cyclopropane). MS m/z (218-100): 218 (M^+, 56%), 203 ($M^+ - CH_3$, 64%), 190 ($M^+ - CO$ and/or C_2H_2, 56%), 189 (31%), 175 (100%), 162 (22%), 161 (58%), 147 (50%), 135 (28%), 134 (36%), 119 (58%), 106 (22%), 105 (56%). IR ($CHCl_3$) ν: 1650 cm^{-1} (enone).

6-Protoilluden-8-ol (9)——A solution of the enone **15** (40 mg) in ether (2.5 ml) was cooled to 0 °C and treated with a cooled solution of LAH (15 mg) in ether (2.5 ml). After 30 min at room temperature, excess LAH was decomposed by adding water–saturated ether. The product was extracted with ether, and the ether solution was washed with brine then dried over anhydrous Na_2SO_4. The ether was removed to give enol **9**, which was purified by silica gel/benzene : acetone=9:1 column chromatography (34 mg, 85% yield). ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.08 (3H, s, CH_3), 1.63 (3H, s, CH_3–C=C), 2.22 (1H, m, proton on C-9), 2.34 (1H, m, proton on C-2), 2.53 (1H, m, proton on C-5), 2.71 (1H, m, proton on C-5), 3.97 (1H, br d, J=8 Hz, proton on C-8). MS m/z: 220 (M^+), 205 ($M^+ - CH_3$), 202 ($M^+ - H_2O$), 191 ($M^+ - C_2H_5$).

8α-Acetoxy-6-protoilludene (26)——Acetylation of **9** (34 mg) with Ac_2O/pyridine at room temperature furnished the acetate **26** (38 mg, 95% yield). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.06 (3H, s, CH_3), 1.47 (3H, s, CH_3–C=C), 2.08 (3H, s, CH_3CO), 5.17 (1H, d, J=8.4 Hz, proton on C-8), 2.5 (1H, m, proton on C-5), 2.7 (1H, m, proton on C-5). MS m/z: 202 ($M^+ - CH_3COOH$), 187 ($M^+ - CH_3COOH - CH_3$), 174 ($M^+ - CH_3COOH - C_2H_2$), 173, 159.

Reduction of 26 to 7-Protoilludene (27)——A solution of **26** (20 mg) in $EtNH_2$ (2 ml) was treated with Li (8 mg) at −78 °C. After the addition, the dry ice–acetone bath was removed and the reaction mixture was stirred for 2 h at room temperature. The $EtNH_2$ was removed and water was added prior to extraction with ether. The ether layer was washed with brine, then dried over Na_2SO_4, and concentrated to give the hydrocarbon **27** (85% yield by GC). ^{1}H-NMR, GC-MS, GC (OV-1: 0.28 mm i.d., 30 m, 150 °C. 9.50 min and OV-17: 0.28 mm i.d., 30 m, 120 °C, 5.15 min) were identical with those of **27** derived from **28**.

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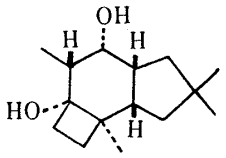
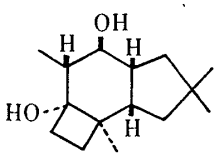


A (major product)



B (minor product)

13) T. Matsumoto, K. Miyano, S. Kagawa, S. Yu, J. Ogawa and A. Ichihara (ref. 9*b*) synthesized *dl*-illudol by way of *cis-anti* methyl 4,4-diethoxy-8-oxo-6-protoilluden-13-oate. This compound was reported to be stable under the dehydration conditions of MsCl–pyridine, 51 °C, 3 h. The difference in epimerization behavior at C-9 between this compound and the enone **15** may be due to the difference of their substituents.
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