123. Multiple *Wagner-Meerwein* Shift. Biogenesis-like Conversion of (±)-$\Delta^{7,8}$-Protoilludene to (±)-Hirsutene and Related Reactions

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Dedicated to Professor Dr. *Conrad Hans Eugster* on the occasion of his 60th birthday

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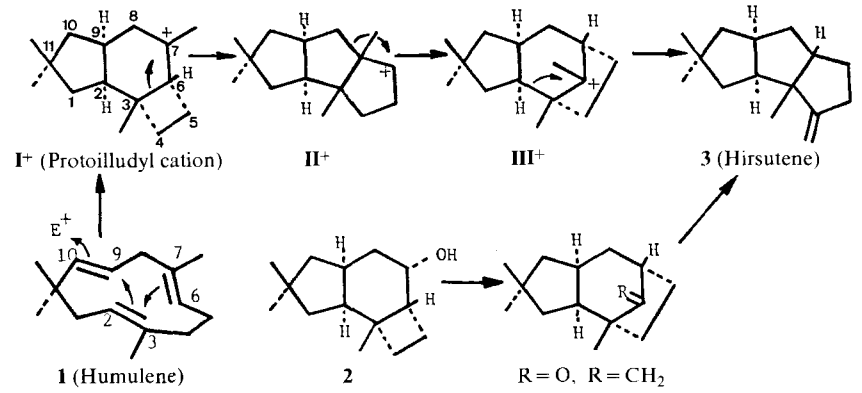
Summary

Experimental details are given for the previous preliminary reports concerning conversion of protoilludane (**28**) to hirsutene (**3**) and related reactions. Treatment of each of the bicyclic analogs **9**, **10**, **12** and **13** of the former compound afforded a hirsutene analog **8**, through multiple 1,2-shift, together with other products. Treatment of a mixture of α- and β-protoilludene -epoxides (**29α** and **29β**) with $BF_3 \cdot Et_2O$ in hexane yielded hirsutane derivatives **30** and **32**. Compound **30** in turn was converted to *endo*-hirsutene **36**, which had already been isomerized to hirsutene (**3**).

Hirsutanoids [1] have been thought to be biosynthesized from humulene (**1**) through protoilludyl cation ($\mathbf{I}^+$) [2] through a triple *Wagner-Meerwein*-shift [3] *(Scheme 1)*. Previously, we reported [4] a synthesis of hirsutene (**3**) [5] starting from

Scheme 1



Note of the Editor. – In the following paper, for nomenclature of hirsutane- and protoilludane derivatives the authors used a special numbering based on the previous numbering of the precursor, humulene (*S. Misumi, Y. Ohfune, A. Furusaki, H. Shirahama & T. Matsumoto*, Tetrahedron Lett. *1976*, 2865). Although this numbering does not conform to the nomenclature rules of IUPAC, we accepted it with consideration of practical reasons. All of the other compounds mentioned in the paper are named according to the IUPAC rules.

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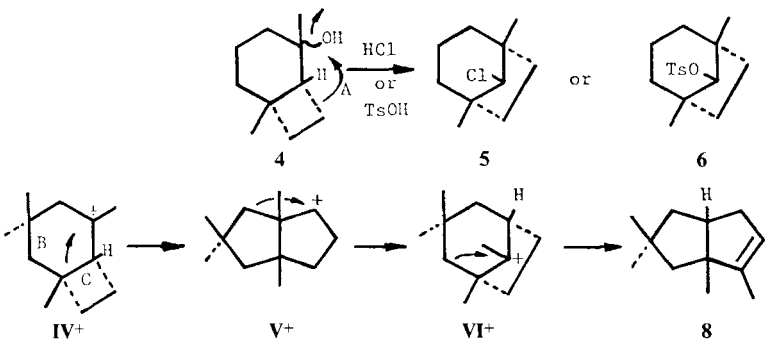
13-norprotoilludan-7α-ol (**2**), but a conversion of protoilludyl cation $\mathbf{I}^+$ or its equivalent to the hirsutene (**3**) has not yet been demonstrated.

According to *Yamada* [6], acid treatment of simple model compound **4** resulted in the formation of undesired bridged compound **5** or **6** through the pathway A *(Scheme 2)*. In the present paper[1]), a reinvestigation of this rearrangement by using four more elaborate model compounds **9**, **10**, **12** and **13** (BC-ring moiety of cation $\mathbf{I}^+$) [7] will be described and then the synthesis of hirsutene (**3**) from 7,8-protoilludene oxide (**29**) [8] will be recorded.

Scheme 2

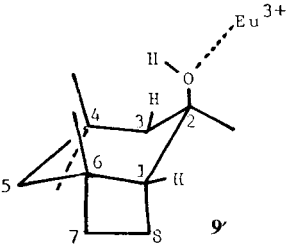


The model compounds **9**, **10**, **12** and **13** were prepared in the following way *(Scheme 3)*. *Grignard* reaction of **7** [9] produced stereoselectively **9** in 96% yield, whose stereostructure was determined by NMR.-spectra[2]) coupled with the use of lanthanide shift reagent, $Eu(fod)_3$. *Wittig* reaction ($Ph_3P{=}CH_2$ benzene) of **7** afforded **10** in 78% yield, which upon epoxidation with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2 and subsequent reduction with LAH in THF at 60° yielded alcohol **12** (80% yield from **10**). Isomerization of the double bond in **10** was achieved with I_2 (0.1 equiv.) in refluxing toluene which gave *endo*-olefinic hydrocarbon **13** in a quantitative yield.

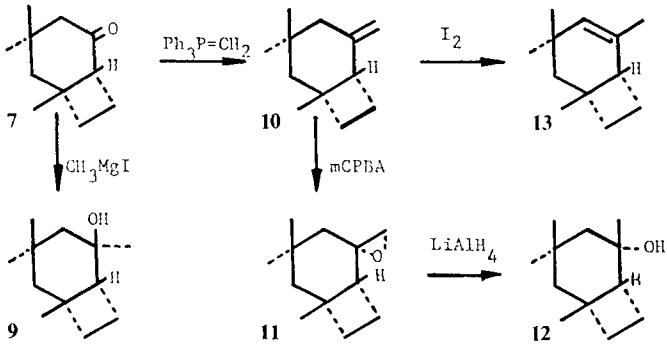
Treatment of each compound, namely **9**, **10** and **12**, with HCO_2H at 0° for 2 h gave a mixture of **13**, **14**, **15**, **8**, **16** and **17** *(Scheme 4)*. On the other hand, similar treatment of **9**, **10**, **12** and **13** at 60° for 0.5 h afforded only the formates **14**, **15** and

[1]) All the compounds described in this paper are racemic.

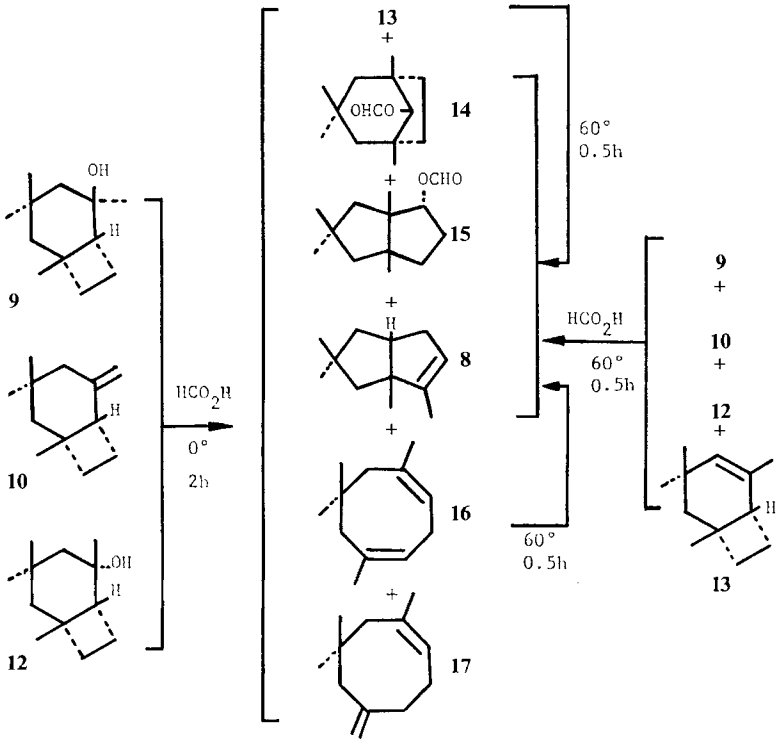
[2]) The LIS./^{1}H-NMR. spectrum [$Eu(fod)_3$:**9** = 0.6, CCl_4] of **9** exhibited peaks at 2.9 (S[10] = 3.8, *s*, 3 H, $(H_3C)_\alpha$–C(4)); 3.56 ($d\times d$, $(J_{7\alpha,8\alpha}+J_{7\beta,8\alpha})/2 = 10$, $(J_{7\alpha,8\beta}+J_{7\beta,8\beta})/2 = 5$, 3 H, $H_{\alpha,\beta}$–C(7)); 3.79 (S = 4.47, *s*, 3 H, H_3C–C(4)); 4.4 (*d*, $J_{5\alpha,5\beta}$ = 13.5, 1 H, H–C(5)); 4.76 (*m*, 1 H, H–C(8)); 4.91 (*d*, $J_{5\alpha,5\beta}$ = 13.5, 1 H, H–C(5)); 5.38 (*m*, 1 H, H–C(8)); 3.82 (*d*, $J_{3\alpha,3\beta}$ = 14, 1 H, H_α–C(3)); 5.84 (S = 7.79, *s*, 3 H, $(H_3C)_\beta$–C(6)); 8.53 (S = 14.08, *s*, 3 H, $(H_3C)_\alpha$–C(2)); 9.6 (S = 15.37, *d*, $J_{3\alpha,3\beta}$ = 14, 1 H, H_β–C(3)); 11.3 (S = 17.54, *t*, $J_{1\beta,8\alpha} = J_{1\beta,8\beta}$ = 10, 1 H, H_β–C(1)). These data are interpreted by a time-averaged conformation **9′** with a quasi-chair, flattened six-membered ring.



Scheme 3



Scheme 4



the hydrocarbon **8**. Although *exo*-olefinic hydrocarbon **17** remained unchanged under the similar reaction conditions as mentioned above, the *endo*-olefinic hydrocarbon **16** afforded the formates **14**, **15** and the hydrocarbon **8**. Yields, product ratios and reaction conditions are summarized in the *Table*.

Separation of the products listed in the *Table* was carried out by chromatography over silica gel, and their structures were determined mainly from spectroscopic data as mentioned below.

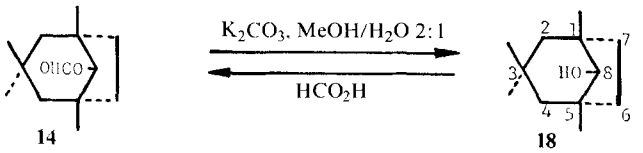
Table. *Treatment of compounds* **9**, **10**, **12**, **13**, **16** *and* **17** *with formic acid*

SM[a])	0°/2 h							60°/0.5 h			
	Y[b])	Product ratios[c])						Y	Product ratios		
		13	**14**	**15**	**8**	**16**	**17**		**14**	**15**	**8**
9	85%	3	4.4	4.4	1	0.2	0.15	88%	1.8	1.8	1
10	81%	2.1	1.6	1.6	1	0.6	0.4	87%	1.4	1.4	1
12	91%	1.9	1.8	1.8	1	0.52	0.38	89%	1.1	1.1	1
13	0%	No reaction						66%	1.1	1.1	1
16								80%	2	2	1
17								0%	No reaction		

[a]) Starting material. [b]) Total yield of the products. [c]) The product ratios were obtained by GLC. or ^{1}H-NMR.

8β-Formyloxy-1β, 3, 3, 5β-tetramethylbicyclo [3.2.1]octane (**14**). – ^{1}H-NMR. (CCl_4): 0.98 and 1.13 (2*s*, each 6 H); 4.53 (*s*, 1 H), 8.08 (*s*, 1 H). – MS.: 210 (M^+). These spectral data showed the presence of partial structure H–OCHO and four tertiary methyl groups. In addition to this the consideration of rearrangement course suggested **14** as a plausible structure for this compound. The configurations of **14** were confirmed by LIS./NMR. studies[3]) of corresponding alcohol **18** obtained from **14** by hydrolysis (*Scheme 5:* K_2CO_3, MeOH/H_2O 2:1) [Eu(fod)$_3$:**18** = 0.105, δ(CCl_4): 1.21 (*S* [10] = 3.0, *s*, 3 H, $(H_3C)_\alpha$–C(3)); 1.47 (*S* = 3.61, *s*, 3 H, $(H_3C)_\beta$–C(3)); 1.65 (*S* = 6.13, *d*, *J* = 13.5, 2 H, H_α–C(2,4)); 1.81 (*S* = 8.4, *s*, 6 H, $(H_3C)_\beta$–C(1,5)); 1.91 (*d*, *J* = 11, 2 H, H_α–C(6,7)); 2.16 (*d*, *J* = 11, 2 H, H_β–C(6,7)); 2.69 (*S* = 10.3, *d*, *J* = 13.5, 2 H, H_β–C(2,4)); 5.71 (*s*, 1 H, H_α–C(8))].

Scheme 5



14 **18**

2α-Formyloxy-1β, 5β, 7, 7-tetramethylbicyclo [3.3.0]octane (**15**). – ^{1}H-NMR. (CCl_4): 1.03 (*s*, 3 H); 1.07 (*s*, 6 H); 1.10 (*s*, 3 H); 4.65 (br. *t*, *J* = 7, 1 H); 7.89 (*s*, 1 H). – MS.: 210 (M^+).

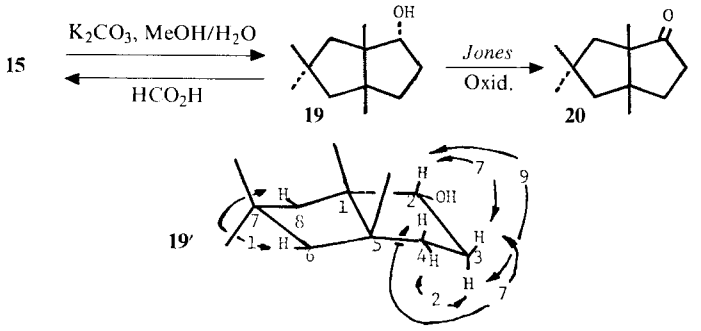
Hydrolysis of **15** (*Scheme 6:* K_2CO_3, aq. MeOH) gave the corresponding alcohol **19** (67% yield), whose ^{1}H-NMR. spectrum showed the presence of partial structure CH(OH)–CH_2 and four tertiary methyl groups. The alcohol **19** gave a compound with cyclopentanone moiety [IR.(neat): 1745] by *Jones* oxidation in 96% yield. These observations and consideration of reaction mechanism suggested structure **15** for this compound; this structure was confirmed by LIS./NMR. spectra of **19**. [Eu(fod)$_3$:**19** = 0.51, δ(CCl_4)]: 1.69 (*s*, 3 H, H_3C–C(7)); 1.76 (*s*, 6 H, H_3C–C(5,7)); 2.30 (*d* × *d*, *J* = 14 and 1, 1 H, H_β–C(6)); 2.52 (*d*, *J* = 14, 1 H, H_α–C(6)); 2.80 (*s*, 3 H, $(H_3C)_\beta$–C(1)); 3.36 (*d* × *d*, *J* = 14 and 1, 1 H, H_β–C(8)); 4.37 (*d* × *qa*, $J_{3\alpha,3\beta}$ = 14,

[3]) LIS = Lanthanide induced shifts.

$J_{3\beta,4\beta}=J_{3\beta,2\beta}=7$, $J_{3\beta,4\alpha}=2$, 1 H, H_α–C(8)); 4,80 (*m*, 1 H, H_α–C(3); 4.82 (*d*, $J=14$, 1 H, H_α–C(8)); 8.05 (*qa*, $J=7$ and 9, 1 H, H_β–C(2)). Extensive spin-decoupling experiments revealed the presence of partial structures $CH_2-CH_2-\overset{H}{\underset{OH}{C}}-$ and $2\,H-\overset{}{C}-H$.

Bicyclo[3.3.0]octane system was, therefore, thought as a most suitable skeleton. Moreover, the observed W-coupling between H_β–C(6) and H_β–C(8) indicated $1\beta,5\beta$-(*cis*)-structure with an approximate conformation **19′**.

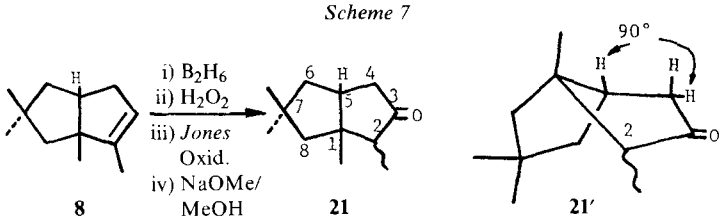
Scheme 6



1, 2, 7, 7-Tetramethyl-cis-*bicyclo [3.3.0]oct-2-ene* (**8**). – ^{1}H-NMR. (CCl_4): 0.98 and 1.01 (2*s*, each 3 H); 1.61 (br.*s*, 3 H); 4.92 (br.*s*, 1 H). – MS.: 164 (M^+). Based on these spectral data partial structures, $HC=\overset{}{C}-CH_3$ and three tertiary methyl groups were obtained and structure **8** was suggested for its compound (see *Scheme 7*). The structure **8** was confirmed by LIS./NMR. studies of cyclopentanone **21** which was obtained from **8** by successive reactions: (i) hydroboration-oxidation (*aq.* NaOH/30% H_2O_2), (ii) *Jones* oxidation (62% yield from **8**) and (iii) equilibration in alkaline medium. Two isomers of **21** with different configuration of H_3C–C(2) were obtained and the major one was used for the LIS. studies. The LIS./NMR. spectrum [Eu(fod)$_3$: **21** = 0.22, CCl_4] of **21** exhibited peaks at 1.72 and 1.76 (2*s*, each 3 H, 2 H_3C–C(7)); 2.66 (*s*, 3 H, $(H_3C)_\beta$–C(1)); 4.21 ($S=15.8$, *d*, $J_{10,2\alpha\text{ or }2\beta}=7$, 3 H, $(H_3C)_{\alpha\text{ or }\beta}$–C(2)); 6.91 ($S=18.6$, *qa*, $J_{2\alpha\text{ or }2\beta,10}=7$, ($H_{\alpha\text{ or }\beta}$–C(2)); ($S=28.9$, *d*, $J_{4\alpha,4\beta}=18.5$, $J_{4\alpha,5\beta}=0$, 1 H, H_α–C(4)); 7.76 ($S=30.8$, *qa*, $J_{4\alpha,4\beta}=18.5$, $J_{4\beta,5\beta}=8$, 1 H, H_β–C(4)). Extensive spin decoupling experiments on the above LIS. spectrum showed the presence of partial structure $-\overset{}{CH}-\underset{CH_3}{\overset{}{C}}(=O)-CH_2$ which was compatible with the bicyclo[3.3.0]octane skeleton. Moreover, J values of $H_{\alpha\text{ or }\beta}$–C(4) indicated a $1\beta,5\beta$-(*cis*)-structure with a probable conformation **21′**. A *trans* analog will not exhibit a coupling constant of about 0 Hz for H_2C(4).

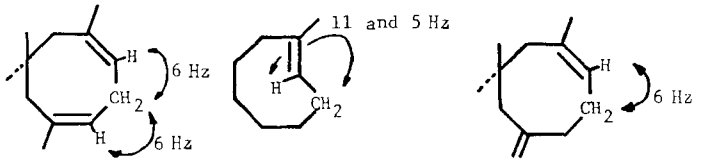
1, 5, 7, 7-Tetramethyl-cis, cis-*1, 4-cyclooctadiene* (**16**). – ^{1}H-NMR. (CCl_4): 0.98 (*s*, 6 H); 1.69 (br.*s*, 6 H); 2.07 (*s*, 4 H); 2.67 (br.*t*, $J=6$, 2 H); 5.37 (br.*t*, $J=6$, 2 H). –

Scheme 7



MS.: 164 (M^+). Based on these data, cyclooctadiene structure **16** could be suggested (see *Scheme 8*). *trans*-Cyclooctene (**22**) has a rather rigid framework and its NMR. signal due to an olefinic proton couples with vicinal methylene protons by 11 and 5 Hz [11]. The NMR. spectrum of our compound showed two olefinic methyl groups as a singlet, two olefinic protons as a triplet ($J = 6$) and a methylene flanked by two double bonds as a triplet ($J = 6$). This coupling constant (6 Hz) corresponds exactly to *cis*-cyclooctenes. It means that the compound have symmetrical and flexible *cis*-diene structure and therefore, formula **16** was assigned.

Scheme 8



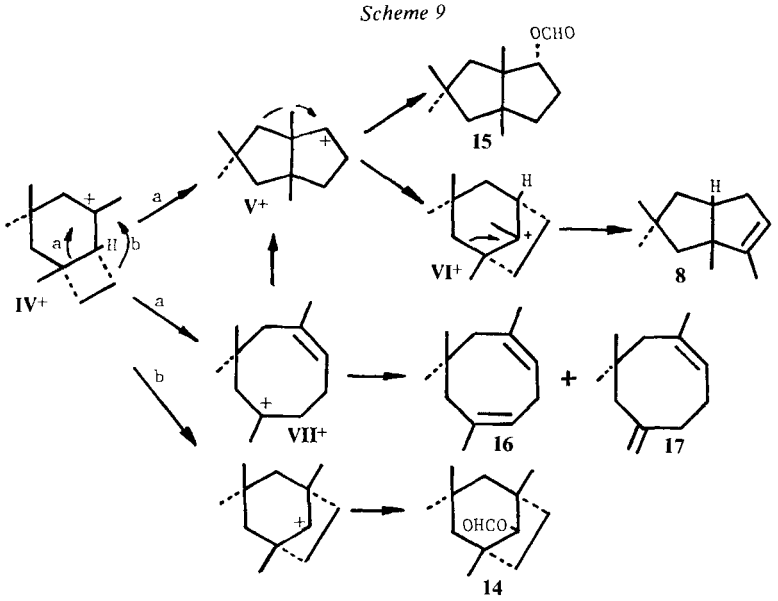
2, 4, 4-Trimethyl-6-methylidene-cis-*1-cyclooctene* (**17**). – ^{1}H-NMR. (CCl_4): 0.98 (*s*, 6 H); 1.72 (br.*s*, 3 H); 1.89 and 1.92 (2*s*, each 2 H); 4.64 (*m*, 2 H); 5.37 (br.*t*, $J = 6$, 1 H). – MS.: 164 (M^+). The spectra together with formation of the compound **16** with this compound suggested formula **17** as a reasonable structure (see *Scheme 8*).

As shown in the *Table*, the *endo*-hirsutene-like hydrocarbon **8** is formed from **16**. Therefore, the reaction proceeded not only through 1,2-shift rearrangements ($\mathbf{IV}^+ \rightarrow \mathbf{V}^+ \rightarrow \mathbf{VI}^+ \rightarrow \mathbf{8}$ in *Scheme 9*), but also through a series of skeletal transformations involving cyclooctyl cation $\mathbf{VII}^+$ as an intermediate ($\mathbf{IV}^+ \rightarrow \mathbf{VII}^+ \rightarrow \mathbf{V}^+ \rightarrow \mathbf{VI}^+ \rightarrow \mathbf{8}$, *Scheme 9*). It is noteworthy that behavior of the cationic species from **4** was different from those the dimethyl analog $\mathbf{IV}^+$. In the latter case, probably, because of the steric crowdedness of the transition state leading to **14** (path b, *Scheme 9*), the reaction is diverted to give other observed products.

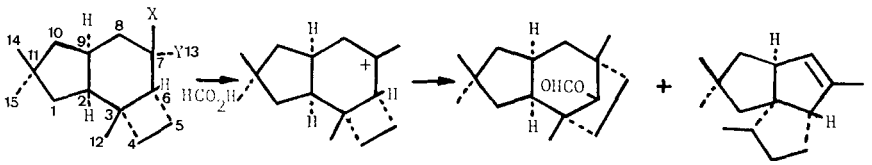
The results obtained in the experiments employing model compounds **9**, **10**, **12** and **13** showed us a possiblity of conversion of the cation $\mathbf{I}^+$ to hirsutene (**3**) along the route similar to biogenesis. Previously, we reported that compounds **23**, **24** and **25** corresponding to the cation $\mathbf{I}^+$ only yielded **26** and **27** [12] (see *Scheme 10*). We checked this time the fate of protoilludyl cation $\mathbf{I}^+$ which was produced by cleavage of 7,8-protoilludene oxides **29**.

Isomerization of double bond of $\Delta^{7,13}$-protoilludene (**25**, *Scheme 11*) [13] was accomplished by treatment with I_2 (0.1 equiv.) in refluxing toluene or by its exposure to MgO (solid base catalyst) [14] in gaseous state to afford $\Delta^{7,8}$-protoilludene (**28**, 93%

Scheme 9



Scheme 10



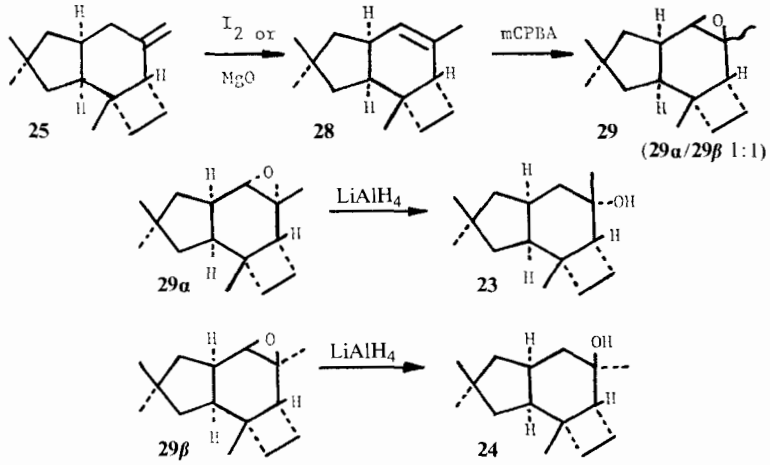
23 X = CH_3, Y = OH (Protoilludyl cation)
24 X = OH, Y = CH_3
25 X = Y = CH_2 **I**+ **26** **27**

yield with I_2 or 100% yield with MgO). Epoxidation of the hydrocarbon **28** gave a pair of stereoisomeric 7,8-protoilludene oxide **29** (**29α/29β** *ca.* 1:1 by GC.), which was separated by preparative TLC. (developing solvent hexane/$CHCl_3$ 1:4) to **29α** and **29β**. The configuration of **29α** and **29β** was determined by reduction of each isomer to the known 7*α*- and 7*β*-protoilludanols[4]) (**23** and **24**) [12] in *ca.* 80% yield respectively.

Rearrangement of the epoxide **29** (isomeric mixture, see *Scheme 11*) was carried out by treatment with a catalytic amount of $BF_3 \cdot OEt_2$ in dry hexane to give **30** (7.1%), **31** (11.3%), **32** (31.4%) and **33** (30.2%). On the other hand, treatment of the separated, pure epoxide **29β** under the similar conditions produced only **33** as a single isolable product (30% yield). The compounds **30**, **31** and **32** were, therefore, formed from the epoxide **29α** *(Scheme 12).*

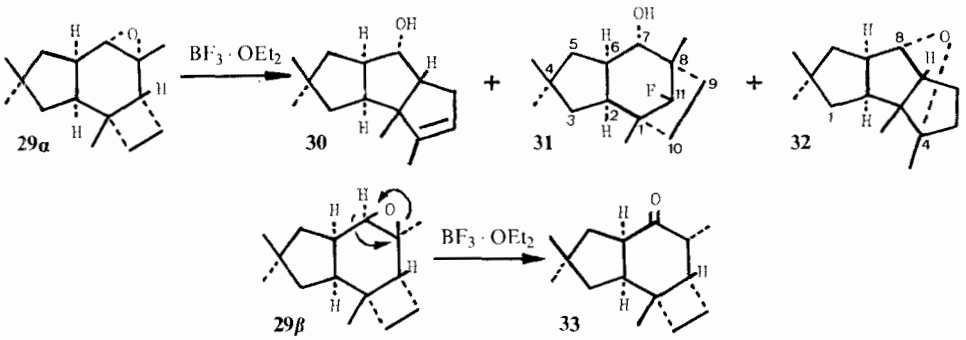
[4]) In this paper C(2) and C(9) protons of protoilludane and hirsutane skeletons are taken to be *α*-oriented.

Scheme 11



25 28 29 (29α/29β 1:1) 29α 23 29β 24

Scheme 12



29α 30 31 32 29β 33

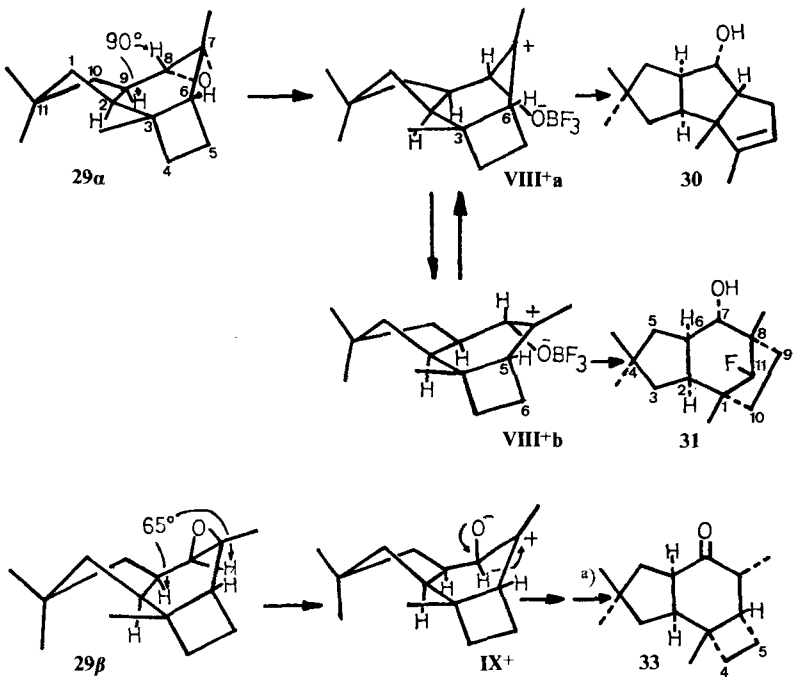
The spectral data of **30** [^{1}H-NMR. (CCl_4): 0.96, 1.02 and 1.10 (3 *s*, each 3 H); 1.75 (br. *s*, 3 H, $H_3C-C=C$); 3.77 (*t*, $J = 7.5$, 1 H); 5.3 (*m*, 1 H, olef. H); IR. (Nujol): 3600–3200. – MS.: 220 (M^+)] suggested that **30** was depicted as *endo*-hirsuten-8α-ol (**30**).

Models show that the cation generated from **29α** can take conformations **VIIIa**$^+$ and **VIIIb**$^+$ (see *Scheme 13*). Since in **VIIIa**$^+$ the vacant orbital at C(7) and C(3), C(6) bond are approximately parallel, and in **VIIIb**$^+$ the vacant orbital at C(7) and C(5), C(6) bond are parallel, the transformations to **30** and **31** are explainable. On the other hand, in the cation **IX**$^+$ furnished from **29β** the H–C(8) bond and the vacant orbital at C(7) are parallel, and therefore **IX**$^+$ is expected to undergo 1,2-hydride shift [15] *(Scheme 13)*.

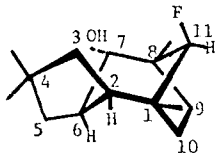
Structures of other products (**31**, **32** and **33**) were deduced chiefly from spectroscopic data as follows.

Data of compound **31**. – ^{1}H-NMR. ($CDCl_3$): 0.98 (*s*, 3 H); 1.10 (*s*, 6 H); 1.12 (*s*, 3 H); 3.56 (*d*, $J = 10.5$, 1 H, H–C(7)); 4.16 (*d*, $J = 53$, 1 H, H–C(11)). – IR. (Nujol):

Scheme 13



3600–3200. The LIS./NMR. spectrum [Eu(fod)$_3$: **31** = 0.3, $CDCl_3$] exhibited peaks at the following positions: 1.41 (*s*, 3 H, $(H_3C)_\alpha$–C(4)); 1.86 (*s*, 3 H, $(H_3C)_\beta$–C(4)); 2.70 (*s*, 3 H, H_3C–C(1)); 3.0 (*d*×*d*, $J_{2\alpha,3\alpha}=6$, $J_{3\alpha,3\beta}=11.5$, 1 H, H_α–C(3)); 3.68 (*m*, 1 H, H_β–C(10)); 4.4 (*d*×*d*, $J_{3\alpha,3\beta}=11.5$, $J_{2\alpha,3\beta}=6$, 1 H, H_β–C(3)); 4.41 (*m*, 1 H, H_β–C(10)); 4.73 (*m*, 1 H, H_β–C(9)); 5.0 (*d*×*t*, $J_{2\alpha,6\alpha}=7$, $J_{2\alpha,3\alpha,\beta}=11.5$, 1 H, H_α–C(2)); 5.26 (*d*×*d*, $J_{5\beta,6\alpha}=6.5$, $J_{5\alpha,5\beta}=13.5$, 1 H, H_β–C(5)); 6.76 (*d*, $J_{11\alpha,F}=53$, 1 H, H_α–C(11)); 7.92 (*S*=20.8, *d*×*d*, $J_{5\alpha,5\beta}=13.5$, $J_{5\alpha,6\alpha}=3.5$, 1 H, H_α–C(5)); 8.33 (*S*=22.8, *m*, 1 H, H_α–C(9)); 10.83 (*S*=29.9, *d*×*d*×*d*, $J_{2\alpha,6\alpha}=7$, $J_{6\alpha,7\beta}=9.5$, $J_{5\alpha,6\alpha}=3.5$, $J_{5\beta,6\alpha}=6.5$, 1 H, H_α–C(6)); 17.18 (*d*, $J_{6\alpha,7\beta}=9.5$, 1 H, H_β–C(7)).



31′: *Approximate conformation of* **31**

Extensive spin-decoupling experiments *(Fig. 1)* showed the presence of partial structure $-CH_2-\underset{}{CH}-\underset{}{CH}-$ which were consistent with formula **31**.

$-CH-\ OH$

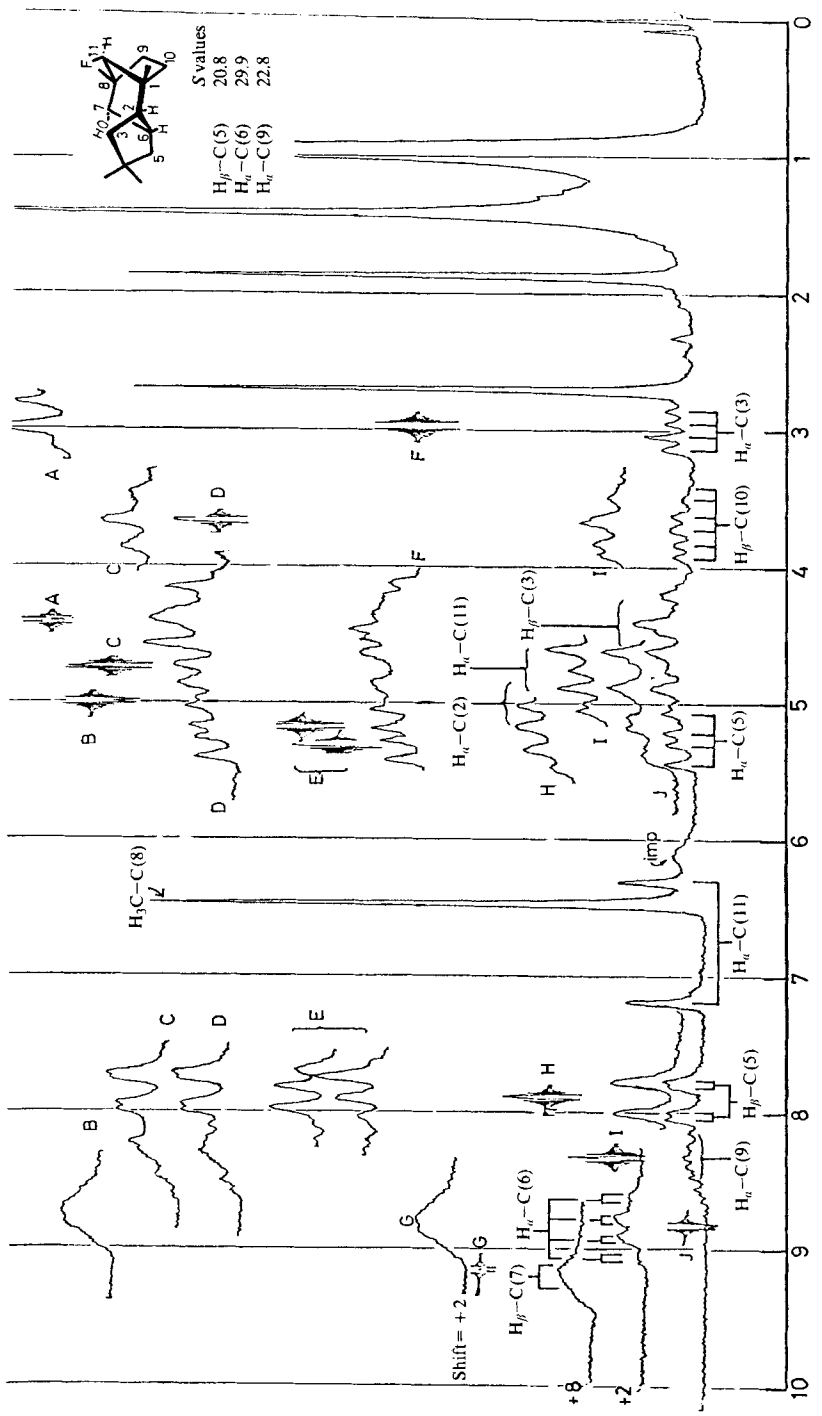
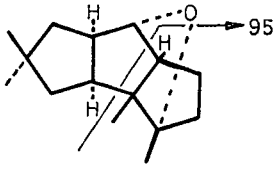
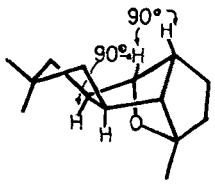


Fig. 1. *^{1}H-NMR. spectrum of* **31** *in the presence of Eu(fod)$_3$ at 60 MHz* (Eu(fod)$_3$:**31** = 0.3, CCl_4)

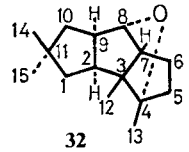
4a,8a-Epoxyhirsutane (**32**). – ^{1}H-NMR. (CCl_4): 0.94, 1.07, 1.18 and 1.26 (4*s*, each 3 H); 2.71 (*m*, 3 H); 3.4 (*s*, 1 H). – MS.: 220 (M^+), 205 ($M^+ - CH_3$), 95 (base peak). Absence of hydroxyl and carbonyl bands in the IR. spectrum and presence of base peak characteristic to hirsutene at *m/z* 95 in its mass spectrum together with consideration of reaction mechanisms suggested the secondary-tertiary ether structure **32** for the rearrangement product. The stereostructure and conformation of **32** were revealed by the following LIS/NMR. data [Eu(fod)$_3$: **32** = 0.314, CCl_4]: 0.71 ($S = -0.8$ [16]; *s*, 3 H, $(H_3C)_a$–C(11)); 1.09 (*s*, 3 H, $(H_3C)\beta$–C(11)); 1.61 (*s*, 3 H, $(H_3C)_\beta$–C(3)); 2.36 (*m*, 2 H, H_2C(1)); 2.41 (*d*×*d*, $J_{10a,10\beta} = 10$, $J_{10\beta,9a} = 7.0$, 1 H, H_β–C(10)); 2.7 (*m*, 1 H, H_β–C(6)); 3.0 (*m*, 1 H, H_β–C(5)); 3.25 (*d*×*d*, $J_{10a,10\beta} = 10$, $J_{10a,9a} = 6.5$, 1 H, H_a–C(10)); 3.72 (*t*, $J_{7\beta,6} = 7$, 1 H, H_β–C(7)); 3.83 (*s*, 3 H, $(H_3C)_\beta$–C(4)); 4.39 ($S = 10.1$, *m*, 1 H, H_a–C(5)); 4.44 ($S = 8.87$, *m*, 1 H, H_a–C(6)); 4.51 ($S = 7.38$, *m*, 1 H, H_a–C(2)); 4.8 ($S = 7.38$, *d*×*d*×*d*, $J_{9a,2a} = 7$, $J_{9a,10a} = 6.5$, $J_{9a,10\beta} = 7$, $J_{9a,8\beta} = 0$, H_a–C(9)); 7.72 (*s*, 1 H, H_a–C(8)). Extensive spin decoupling experiments on the above LIS. spectra elucidated the existence of partial structures



32



32'

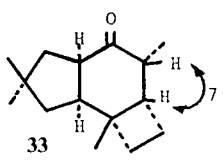


32

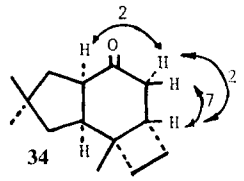
Fig. 2. *S-values of main NMR. signals of* **32**

which were in accordance with the structure **32**. Moreover, relatively large lanthanide-induced shift value of signals due to H_α–C(2) ($S = 7.38$), H_α–C(9) ($S = 7.38$), H_α–C(6) ($S = 8.87$), H_α–C(5) ($S = 10.1$) and upfield induced shift of the $(H_3C)_\alpha$–C(11) peak ($S = -0.8$) as well as the singlet nature of the H_β–C(8) signal could indicate conformation **32'** *(Fig. 2)*.

8-Oxoprotoilludane (**33**). – ^{1}H-NMR. (CCl_4): 0.89 (*d*, $J = 7$, 3 H); 0.98, 1.09 and 1.2 (3*s*, each 3 H); 2.94 (*qi*, $J = 7$, 1 H); 2.95 (*d*×*t*, $J = 7.5$ and 8, 1 H). – IR. (neat): 1710. The double resonance NMR. and IR. spectra of **33** showed the presence of partial structure $-CH_2-\underset{|}{CH}-\underset{\|}{C}-\underset{|}{CH}-CH-$ and accordingly structure **33** was
$-CH-O \quad CH_3$
assigned. Comparison of the LIS./NMR. spectrum [*Fig. 3*, Eu(fod)$_3$: **33** = 0.24, CCl_4] with that of 8-oxo-13-norprotoilludane (**34**) [13] [*Fig. 4*, Eu(fod)$_3$: **34** = 0.22, CCl_4] indicated that the two compounds had an almost identical flattened cyclohexanone conformation and the $J_{6\beta,7\beta}$ value (7 Hz) of both compounds showed the H_3C–C(7) group of **33** to have the thermodynamically stable α-configuration (C(10)/H_3C–C(7) *trans*)[5]).

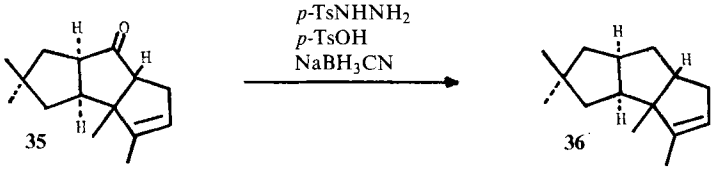


33



34

Jones oxidation of **30** furnished cyclopentanone derivative **35** in 84.7% yield [^{1}H-NMR. (CCl_4): 0.98, 1.05 and 1.22 (3*s*, each 3 H); 1.72 (br.*s*, 3 H); 5.22 (br.*s*, 1 H). – IR. (neat): 1740]. Treatment of **35** with *p*-TsNHNH$_2$ followed by reduction with $NaBH_3CN$ and a catalytic amount of *p*-TsOH in DMF/sulfolane 1:1 [17] at 110° (4 h) afforded *endo*-hirsutene (**36**), which was identical in all respects with the authentic sample [4]. Since *endo*-hirsutene has already been converted to the natural hirsutene (**3**) by us [4], the present experiment means the first *in vitro* conversion of $\Delta^{7,8}$-protoilludene (**28**) to hirsutene (**3**).



35 **36**

endo-Hirsutene

[5]) In the previous paper [8] the β-configuration was erroneously assigned for H_3C–C(7) of **33**.

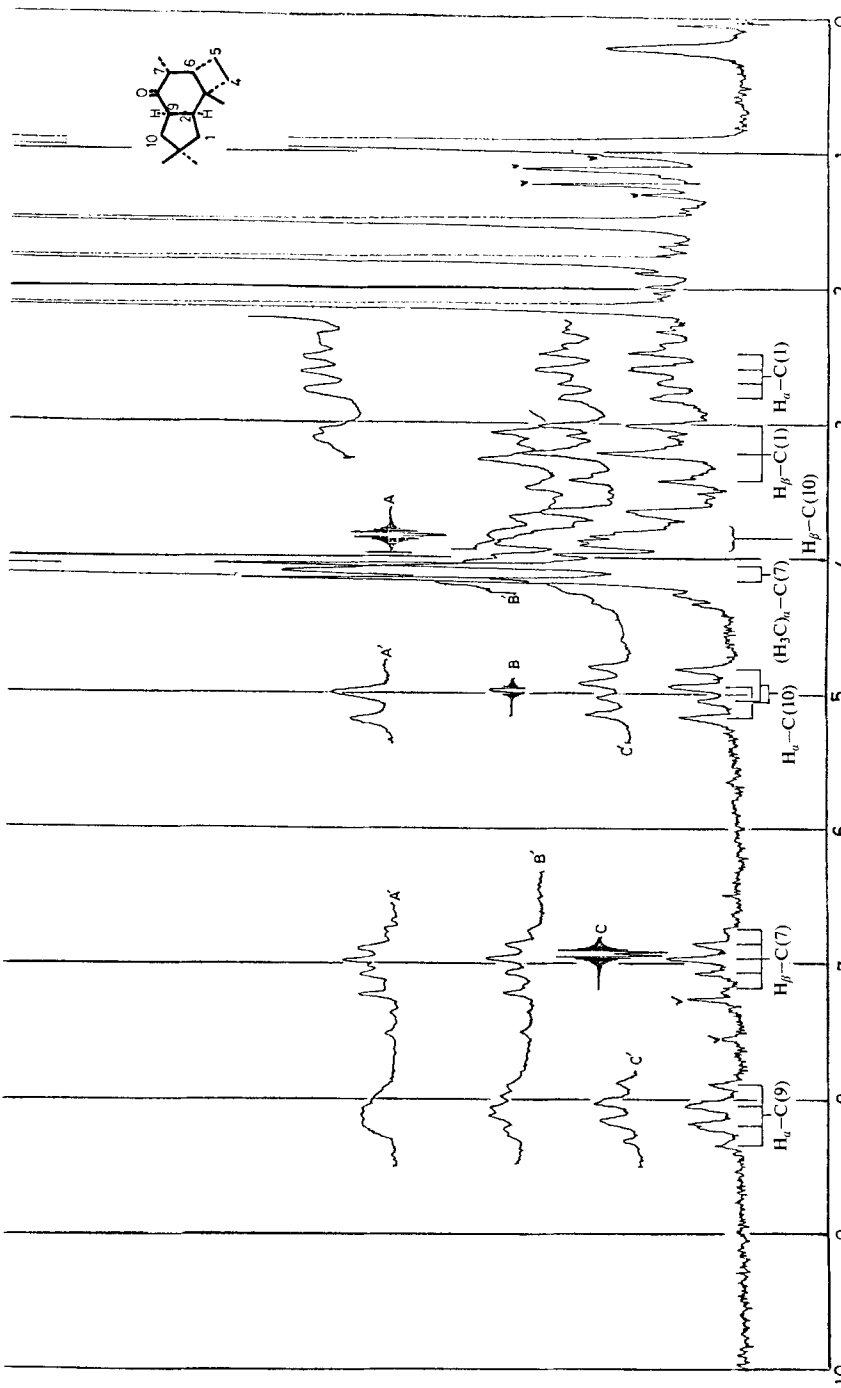


Fig. 3. *^{1}H-NMR. spectrum of* **33** *in the presence of Eu(fod)$_3$ at 60 MHz* (Eu(fod)$_3$: **33** = 0.24, CCl_4)

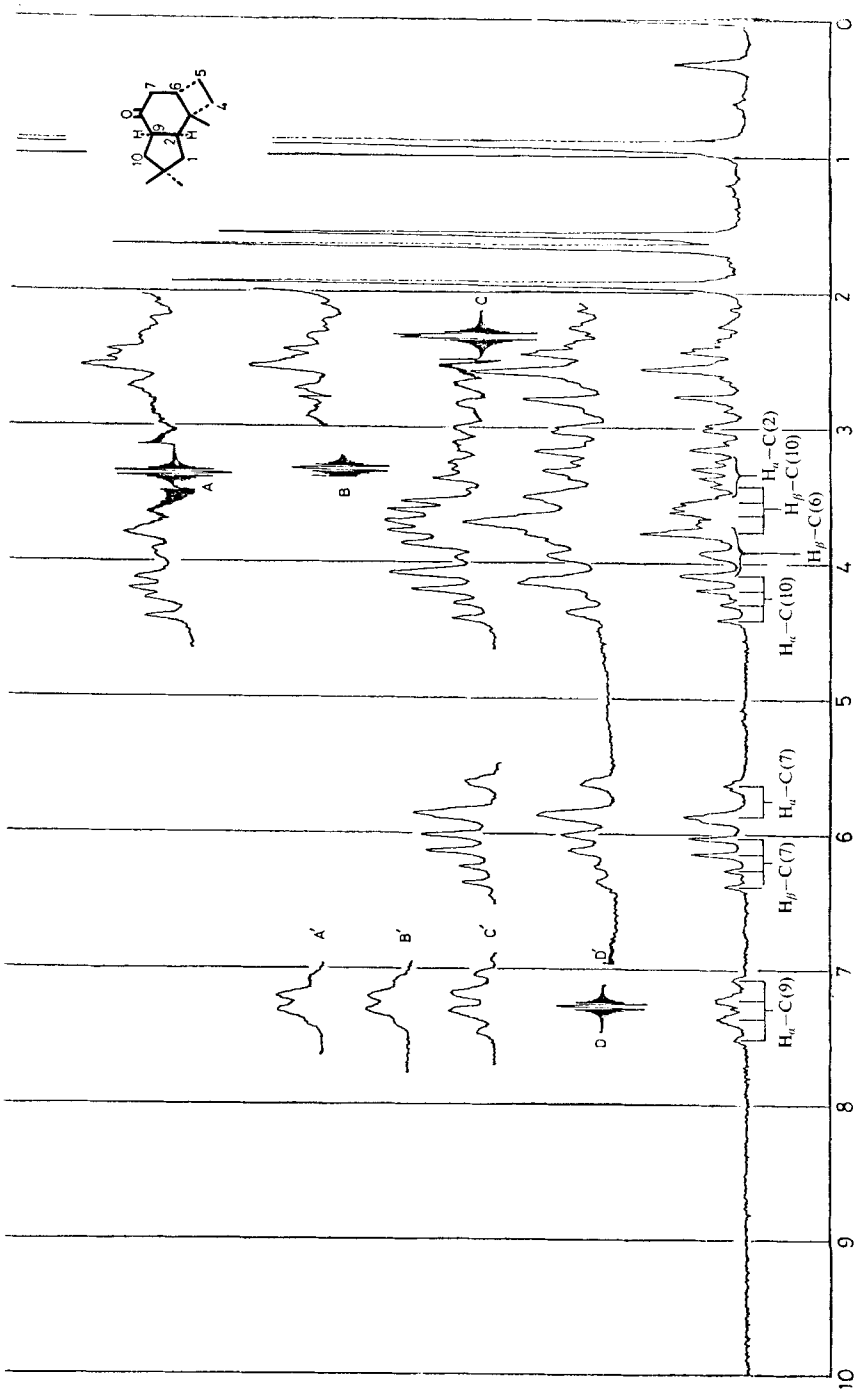


Fig. 4. *^{1}H-NMR. spectrum of* **34** *in the presence of Eu(fod)$_3$ at 60 MHz* (Eu(fod)$_3$: **34** = 0.22, CCl_4)

Experimental Part

General. Melting points were determined in open capillaries and are uncorrected. ^{1}H-NMR. spectra were measured at 60 MHz on a *Hitachi* R20B instrument and at 100 MHz on a *Jeolco* PS100 instrument. Chemical shifts are reported in δ units relative to internal TMS. IR. spectra were measured on a JASCO IR-S instrument and were calibrated with 1603 cm^{-1} absorption of polystyrene. Low-resolution mass spectra were obtained with a *Hitachi* RMS-6U instrument. GLC. analysis were performed on a *Hitachi* 063 employing 1 m × 3 mm column packed with 20%-Silicone QF-1. Elemental analyses were performed in Laboratory for Instrumental Analysis of Hokkaido University. Abbreviation: RT. = room temp., i.V. = *in vacuo*, HV. = high vacuum.

2α,4,4,6β-Tetramethyl-cis-*bicyclo[4.2.0]octan-2-ol* (**9**). A solution of 4,4,6-trimethyl-*cis*-bicyclo[4.2.0]octan-2-one (**7**) (1.3 g, 7.83 mmol) in 10ml of dry ether was added to a cooled solution of CH_3MgI in dry ether [prepared from Mg (0.4 g, 16.7 mmol) and CH_3I (2.8 g, 19.7 mmol) in 8 ml of dry ether] with stirring over a period of about 5 min. The mixture was stirred for 2 h at 0° and quenched by addition of ice and water, and then acidified with 6N HCl. The ether layer was separated, and the aqueous layer was extracted twice with ether. The combined extracts were washed twice with $NaHCO_3$-solution, dried over Na_2SO_4, and the ether was removed i.V. The residual solid was chromatographed on silicagel column (eluent hexane/EtOAc 98:2) to give 1.37 g (96%) of **9**: m.p. 52–54°. – ^{1}H-NMR. (CCl_4): 0.92, 0.93, 1.12 and 1.20 (4*s*, each 3 H). – IR. (Nujol): 3600–3200. – MS.: 167 ($M^+ - CH_3$), 164 ($M^+ - H_2O$), 149 ($M^+ - CH_3 - H_2O$).

$C_{12}H_{22}O$ (182.30) Calc. C 79.06 H 12.16% Found C 79.21 H 12.18%

4,4,6-Trimethyl-2-methylidene-cis-*bicyclo[4.2.0]octane* (**10**). A solution of the ketone **7** (868 mg, 5.23 mmol) in 2 ml of dry benzene was added at RT. to a stirred solution of $Ph_3P{=}CH_2$ in dry benzene [prepared from *t*-AmONa (610 mg, 5.55 mmol) and Ph_3PCH_3Br (1.96 g, 5.51 mmol) in 10 ml of dry benzene]. After stirring at RT. for 2 h, the mixture was quenched by addition of water, and extracted 3 times with hexane. The combined extracts were washed with water and brine, dried over Na_2SO_4, and evaporated i.V. The residual oil was passed through a short column of silicagel (eluent hexane) to furnish 670 mg (78%) of **10**. – ^{1}H-NMR. (CCl_4): 0.79, 0.98 and 1.10 (3*s*, each 3 H); 4.54 (*m*, 2 H). – IR. (neat): 3100, 1650 and 890. – MS.: 164 (M^+).

$C_{12}H_{20}$ (164.28) Calc. C 87.73 H 12.27% Found C 87.61 H 12.32%

2β,4,4,6β-Tetramethyl-cis-*bicyclo[4.2.0]octan-2-ol* (**12**). To a stirred solution of **10** (200 mg, 1.22 mmol) in 8ml of CH_2Cl_2 was added 250 mg (1.45 mmol) of *m*-CPBA at RT. After 1.5 h at RT., the reaction mixture was quenched by addition of aq. $Na_2S_2O_3$-solution and 3N NaOH, and extracted 3 times with CH_2Cl_2. The extracts were washed with water and brine, and dried over Na_2SO_4. Removal of the solvent gave crude epoxides, which were reduced with LAH (50 mg, 1.32 mmol) in 10 ml of dry THF (60°, 1 h) under Ar. The reaction mixture was then cooled to 0°, quenched by addition of ice, diluted with ether, and dried over Na_2SO_4. After filtration, removal of the solvent gave crude alcohols, which were chromatographed on silicagel column (eluent hexane/EtOAc 97:3) to afford 39 mg (17.8%) of **9** and 177 mg (80%) of **12**. – IR. (neat): 3600–3200. – ^{1}H-NMR. (CCl_4): 0.97, 1.01, 1.16 and 1.18 (4*s*, each 3 H). – MS.: 182 (M^+), 164 ($M^+ - H_2O$), 149 ($M^+ - H_2O - CH_3$).

$C_{12}H_{22}O$ (182.30) Calc. C 79.06 H 12.16% Found C 79.32 H 12.14%

2,4,4,6-Tetramethyl-cis-*bicyclo[4.2.0]oct-2-ene* (**13**). A solution of **10** (200 mg, 1.22 mmol) and I_2 (30 mg, 0.12 mmol) in 8 ml of dry toluene was refluxed for 4.5 h under Ar. The reaction mixture was then cooled to 0°, washed with aq. $Na_2S_2O_3$-solution and brine, and dried over Na_2SO_4. Removal of the solvent under reduced pressure left a crude oil, which was passed through a short column of silicagel (eluent hexane) to give 200 mg (quantitative yield) of **13** as an oil. – IR. (neat) 790. – ^{1}H-NMR. (CCl_4): 0.97, 1.03 and 1.19 (3*s*, each 3 H); 1.54 (br.*s*, 3 H); 5.10 (br.*s*, 1 H). – MS.: 164 (M^+).

$C_{12}H_{20}$ (164.28) Calc. C 87.73 H 12.27% Found C 87.80 H 12.25%

Formolysis of **9**, **10**, **12** *and* **13** *at 60°.* A stirred solution of **9** (140 mg, 0.769 mmol) in 9 ml of HCO_2H/Ac_2O 3:1 was heated at 60° for 30 min under Ar. The reaction mixture was then cooled to 0° diluted with water, and extracted 4 times with hexane. The combined extracts were washed with aq. $NaHCO_3$-solution and brine, and dried over Na_2SO_4. Removal of the solvent gave crude oil, whose GLC. (20% QF-1, 150°) showed three peaks due to formates **14**, **15** and hydrocarbon **8** (**14**/**15**/**8** 1.8:1.8:1). The crude oil was separated through silicagel column using hexane followed by hexane/EtOAc 97:3 as eluents to give 24.0 mg (19.1%) of **8** and 111.0 mg (68.9%) of a mixture of **14** and **15**.

Data of **8**. – For spectral data see text.

$C_{12}H_{20}$ (164.28) Calc. C 87.73 H 12.27% Found C 87.52 H 12.36%

Results of formolysis (60°, 1 h) of **10**, **12**, **13**, **16** and **17** were examined by similar experiments. The product ratio was obtained by GC. These results are summarized in the *Table*.

Hydrolysis of the formates **14** *and* **15**. A solution of the formates **14** and **15** (111.0 mg, 0.53 mmol) and K_2CO_3 (76 mg, 0.55 mmol) in 12 ml of H_2O/MeOH 1:2 was stirred for 2.5 h at RT. The mixture was concentrated i.V. diluted with water, extracted 3 times with ether, and the extracts were washed with brine, and dried over Na_2SO_4. Removal of the solvent gave a crude product, which was chromatographed on silicagel column (eluent hexane/EtOAc 97:3) to give 32.5 mg (33.5%) of 1β,3,3,5β-tetramethylbicyclo[3.2.1]octan-8β-ol (**18**) and 32.0 mg (33.4%) of 1β,5β,7,7-tetramethylbicyclo[3.3.0]octan-2α-ol (**19**).

Data of **18**: m.p. 41–42°. – ^{1}H-NMR. (CCl_4): 0.9 (*s*, 12 H); 1.08 (*s*, 4 H); 2.97 (*s*, 1 H). – IR. (Nujol): 3600–3200. – MS.: 182 (M^+), 167 ($M^+ - CH_3$).

$C_{12}H_{22}O$ (182.30) Calc. C 79.06 H 12.16% Found C 79.11 H 12.07%

Data of **19**. – ^{1}H-NMR. (CCl_4): 1.0 and 1.04 (2*s*, each 3 H); 1.08 (*s*, 6 H); 3.51 (*qa*, J = 7 and 9, 1 H). – IR. (neat): 3600–3200. – MS.: 182 (M^+), 167 ($M^+ - CH_3$).

$C_{12}H_{22}O$ (182.30) Calc. C 79.06 H 12.16% Found C 78.90 H 12.18%

Preparation of 8β-formyloxy-1β,3,3,5β-tetramethylbicyclo[3.2.1]octane (**14**). A mixture of **18** (50 mg, 0.275 mmol) and 3 ml of HCO_2H was heated at 60° for 1 h under Ar. The mixture was then cooled to 0°, diluted with water and extracted 3 times with hexane, and the extracts were washed with aq. $NaHCO_3$-solution and brine, and dried over Na_2SO_4. Removal of the solvent gave a crude oil, which was chromatographed on silicagel column (eluent hexane/EtOAc 97:3) to give 53.0 mg (92%) of **14**. For spectral data see text.

$C_{13}H_{22}O_2$ (210.31) Calc. C 74.24 H 10.54% Found C 74.26 H 10.28%

Preparation of 2α-formyloxy-1β,5β,7,7-tetramethylbicyclo[3.3.0]octane (**15**). Treatment of **19** (50 mg, 0.275 mmol) with HCO_2H was done by the same method described above. The product was separated by column chromatography on silicagel (eluent hexane/EtOAc 97:3) to give 55.5 mg (96%) of **15**. – ^{1}H-NMR.: see text.

$C_{13}H_{22}O_2$ (210.31) Calc. C 74.24 H 10.54% Found C 74.40 H 10.63%

1β,5β,7,7-Tetramethylbicyclo[3.3.0]octan-2-one (**20**). To a stirred and cooled solution of **19** (50 mg, 0.275 mmol) in 6 ml of acetone was added slowly *Jones* reagent ($H_2Cr_2O_7$) until the orange color of the reagent persisted for about 20 min. The excess oxidizing agent was destroyed by addition of a small quantity of *i*-PrOH. After removal of solid, $NaHCO_3$ was added to the solution with swirling until evolution of CO_2 ceased. The suspension was filtered, and the filtrate was evaporated to give crude product, which was separated by column chromatography on silicagel (eluent hexane/EtOAc 97:3) to afford 55.5 mg (95.9%) of **20**. – IR. (neat): 1745. – ^{1}H-NMR. (CCl_4); 0.85 and 0.93 (2*s*, each 3 H); 1.08 (*s*, 6 H); 1.38 (*d*, J = 13, 1 H); 2.02 (*d*, J = 13, 1 H). – MS.: 180 (M^+).

$C_{12}H_{20}O$ (180.38) Calc. C 79.94 H 11.18% Found C 79.96 H 11.42%

Treatment of **9**, **10**, **12** *and* **13** *with formic acid at* 0°. A solution of **9** (5.5 g, 30.22 mmol) in 150 ml of HCO_2H/Ac_2O 3:1 was stirred for 2 h at 0° under Ar. The mixture was diluted by addition of water and extracted 4 times with hexane. The extracts were washed with aq. $NaHCO_3$-solution and brine, and dried over Na_2SO_4. Removal of the solvent gave crude product, which was chromatographed on silica-gel column using hexane followed by hexane/EtOAc 97:3 as eluents to give 1.4 g (28.3%) of a mixture of hydrocarbons whose ratio was determined by the NMR. integration of the mixture (**13**/**8**/**16**/**17** 3:1:0.25:0.15) and 3.6 g (56.7%) of the mixture of formates **14** and **15** whose ratio was shown by GC. analysis (20% QF-1, 150°) as 1:1. The hydrocarbons were separated through column of silica-gel impregnated with 10% $AgNO_3$ to give 950 mg of **13**, 310 mg of **8**, 79 mg of **16** and 47 mg of **17**.

Results of the analogous treatment (0°, 2 h) of **10**, **12** and **13** were examined by similar experiments. The product ratios were obtained by GC. analysis and NMR. integration, and summarized in the *Table*.

Data of **16**. – ^{1}H-NMR.: see text.

$C_{12}H_{20}$ (164.28) Calc. C 87.73 H 12.27% Found C 87.64 H 12.24%

Data of **17**. – ^{1}H-NMR.: see text.

$C_{12}H_{20}$ (164.28) Calc. C 87.73 H 12.27% Found C 87.61 H 12.27%

Hydroboration and oxidation of the hydrocarbon **8**; *preparation of 1,2,7,7-tetramethyl-*cis*-bicyclo-[3.3.0]octan-3-one* (**21**). To a stirred solution of **8** (159 mg, 0.97 mmol) in 3 ml of dry THF was added 1.5 ml of $BH_3 \cdot$ THF complex (1M in THF) at 0° under Ar. After stirring at RT. for 3 h, the excess diborane was decomposed by addition of 1 ml of water and the organoborane was oxidized by adding 1 ml of 3N NaOH, followed by dropwise addition of 1 ml of 30% H_2O_2-solution to the stirred solution at RT. After stirring for an additional hour, the mixture was extracted 3 times with ether and the extracts were washed with brine and dried over Na_2SO_4. Removal of the solvent gave crude product, which was dissolved in 20 ml of acetone and oxidized by *Jones* reagent at RT. to give an epimeric mixture (concerning $H_3C-C(2)$) of ketones. Equilibration of the epimeric ketone was done by treating it with 10 ml of 0.1% NaOMe/MeOH for 1 h at RT. and then chromatographic separation (eluent hexane/EtOAc 97:3) gave 108 mg (62% from **8**) of **21**. – IR. (neat): 1745. – ^{1}H-NMR. (CCl_4): 0.88 (*d*, $J = 7$, 3 H)); 0.91 (*s*, 3 H); 1.1 (*s*, 6 H). – MS.: 180 (M^+).

$C_{12}H_{20}O$ (180.28) Calc. C 79.94 H 11.18% Found C 79.72 H 11.12%

7,8-Protoilludene oxides (**29**) *and separation of* **29α** *and* **29β**. A solution of **28** [13] (1.04 g, 5.15 mmol) and *m*-CPBA (85%, 1.24 g, 6.12 mmol) in 80 ml of dry CH_2Cl_2 was stirred for 1.5 h at 0°. The reaction mixture was successively washed with aq. $Na_2S_2O_3$- and aq. NaOH-solutions and brine, and dried over Na_2SO_4. After removal of the solvent i.V., resulting oil was purified by chromatography on silicagel (eluent hexane/EtOAc 97:3) to give 1.10 g (98%) of **29** (**29α**/**29β** ≈ 1:1). The epoxides (100 mg) were separated by preparative TLC. (developing solvent hexane/$CHCl_3$ 1:4) to afford 12 mg of **29α** the less polar compound [^{1}H-NMR. (CCl_4): 1.02 (*s*, 6 H); 1.13 (*s*, 3 H); 1.22 (*s*, 3 H); 2.56 (*s*, 1 H). – MS.: 220 (M^+)] and 16 mg of **29β**, the more polar compound [^{1}H-NMR. (CCl_4): 0.97 (*s*, 3 H); 1.09 (*s*, 6 H); 1.19 (*s*, 3 H); 2.75 (*d*, $J = 1.5$, 1 H). – MS.: 220 (M^+)].

Reduction of **29α** *and* **29β** *to 7α-protoilludanol* (**23**) *and 7β-protoilludanol* (**24**). A solution of **29α** (12 mg, 0.055 mmol) and $LiAlH_4$ (5 mg, 0.13 mmol) in 2 ml of dry THF was stirred for 16 h at 0° under Ar. The reaction mixture was diluted by Et_2O (2 ml) and quenched by addition of ice and the etheral layer was dried over Na_2SO_4. After filtration, the filtrate was concentrated i.V. to give a crude oil, which was purified by chromatography on silicagel (eluent hexane/EtOAc 96:4) to yield 9.5 mg (*ca.* 80%) of **23**.

The reduction of **29β** (16 mg, 0.073 mmol) to **24** was done by the same method described above. Chromatographic separation of the crude product (eluent hexane/EtOAc 96:4) gave 12.5 mg (*ca.* 80%) of **24**.

Spectral data of both **23** and **24** were in complete agreement with those reported [12].

Rearrangement of **29** *(isomeric mixture,* **29α**/**29β** ≈ 1:1) *with* $BF_3 \cdot OEt_2$ *in dry hexane.* To a stirred and cooled solution of **29** (830 mg, 3.77 mmol) in 20 ml of dry hexane was added dropwise 8 drops (0.05 ml, 0.396 mmol) of $BF_3 \cdot OEt_2$ at 0° under Ar. The reaction mixture was stirred for 20 min at 0°, quenched by addition of aq. $NaHCO_3$-solution, and extracted 3 times with ether. The extracts were washed with brine, and dried over Na_2SO_4. Removal of the solvent i.V. gave a crude oil, which was separated by chromatography on silicagel using EtOAc/hexane 1:99 followed by EtOAc/hexane 3:97 as eluents to give **30** (59 mg, 7.1%), **31** (102.5 mg, 11.3%), **32** (261 mg, 31.4%) and **33** (251 mg, 30.2%).

Data of endo*-hirsuten-8α-ol* (**30**). – M.p. 36–37°. – IR. and ^{1}H-NMR.: see text. – MS.: 220 (M^+), 202 ($M^+ - H_2O$), 94 (base peak).

$C_{15}H_{24}O$ (220.34) Calc. C 81.76 H 10.98% Found C 81.55 H 10.90%

*Data of (1*RS,*2*SR,*6*RS,*7*SR,*8*SR,*11*SR*)-11-fluoro-1,4,4,8-tetramethyltricyclo[6.2.1.0^{2,6}]undecan-7-ol* (**31**). – M.p. 105–107°. – IR. and ^{1}H-NMR.: see text. – MS.: 225 ($M^+ - CH_3$), 96 (base peak).

$C_{15}H_{25}FO$ (240.34) Calc. C 74.95 H 10.48% Found C 74.65 H 10.69%

Data of 4α,8α-epoxyhirsutane (**32**). – ^{1}H-NMR.: see text. – MS.: 220 (M^+), 205 ($M^+ - CH_3$), 95 (base peak).

$C_{15}H_{24}O$ (220.34) Calc. C 81.76 H 10.98% Found C 81.62 H 11.10%

Data of 8-Oxoprotoilludane (**33**). – IR. and ^{1}H-NMR.: see text. – MS.: 220 (M^+), 192 ($M^+ - C_2H_4$, base peak).

$C_{15}H_{24}O$ (220.34) Calc. C 81.76 H 10.98% Found C 81.55 H 11.10%

Preparation of endo-*hirsuten-8-one* (**35**). To a stirred and cooled solution of **30** (147 mg, 0.668 mmol) in 18 ml of acetone was added slowly *Jones* reagent until the orange color of the reagent persisted for 30 min. The excess oxidizing agent was destroyed by addition of a small quantity of *i*-PrOH. After removal of solid, $NaHCO_3$ was added to the solution with swirling until evolution of CO_2 ceased. The suspension was filtered, and the filtrate was evaporated to give crude product, which was separated by chromatography on silicagel (eluent hexane/EtOAc 99:1) to give 123.5 mg (84.7%) of **35**. – IR. (neat): 1710, 813. – ^{1}H-NMR. (CCl_4): 0.98, 1.05 and 1.22 (3*s*, each 3 H); 1.72 (br.*s*, 3 H); 5.22 (*m*, 1 H). – MS.: 218 (M^+), 94 (base peak).

$C_{15}H_{22}O$ (218.33) Calc. C 82.51 H 10.16% Found C 82.48 H 10.20%

Preparation of endo-*hirsutene* (**36**). A solution of **35** (123.5 mg, 0.566 mmol) and *p*-$TsNHNH_2$ (126 mg, 0.676 mmol) in 9 ml of abs. ethanol was refluxed for 2 days under Ar. The reaction mixture was then cooled to RT. and evaporated i.V. To the resulting crude tosylhydrazone was added 9 ml of dimethylformamide/sulfolane 1:1, 15 mg (0.079 mmol) of *p*-TsOH and 142 mg (2.25 mmol) of $NaBH_3CN$ [17]. The mixture was heated to 110° for 4 h under Ar, cooled to 0°, diluted by addition of water, and extracted 4 times with benzene. The extracts were washed with water and brine, and dried over Na_2SO_4. Removal of the solvent gave a crude oil, which was separated by chromatography on silicagel using hexane followed by EtOAc/hexane 2:98 as eluents to afford 9.0 mg (*ca.* 8%) of **36** and 13 mg (13%) of starting material **35**.

Data of **36**. – IR. (neat): 1653, 803. – ^{1}H-NMR. (CCl_4): 0.96, 0.97 and 1.08 (3*s*, each 3 H); 1.6 (br.*s*, 3 H); 5.01 (br.*t*, $J = 2.5$, 1 H). – MS.: 204 (M^+), 189 ($M^+ - CH_3$), 94 (base peak).

These spectral data were in complete agreement with those of an authentic sample [4].

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