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SYNTHESIS OF PENTALENIC ACID THROUGH BIOGENETIC LIKE CYCLIZATION OF HUMULENE

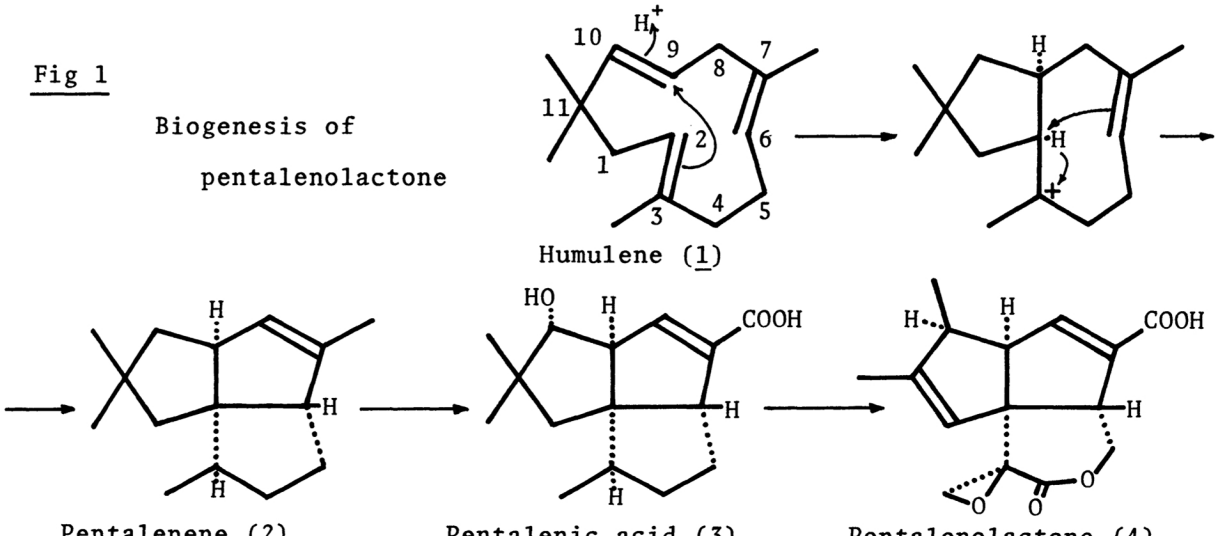
Kazuya SAKAI, Toshikazu OHTSUKA, Shunjiro MISUMI,
Haruhisa SHIRAHAMA* and Takeshi MATSUMOTO*
Department of Chemistry, Faculty of Science,
Hokkaido University, Sapporo 060

Summary: Humulene furnished 4,7-epoxy-3-methylene-7,10,10-trimethyl-11-bicyclo[6,3,0]undecanol 9 in 34% yield employing oxymercuration as a key step. On treatment with $BF_3 \cdot OEt_2$, 7,11-dihydroxy-3,7,10,10-tetramethyl-3-bicyclo[6.3.0]undecene, which was derived from 9 by ether cleavage, afforded 10α-hydroxy-pentalenene 13 (20%) along with four byproducts. Oxidation of allylic methyl group of 13 gave methyl pentalenate in 13% yield from 9.

An antibiotic fungus metabolite, pentalenolactone (4) has recently been aimed as an attractive target of synthetic works.[1] The compound was demonstrated[2] to be biosynthetically derived from humulene (1) and several compounds which are thought to be biosynthetically intervened between 1 and 4 were isolated.[3] We are currently interested in the biogenetic like synthesis of the sesquiterpenes

Fig 1

Biogenesis of pentalenolactone



Humulene (1)

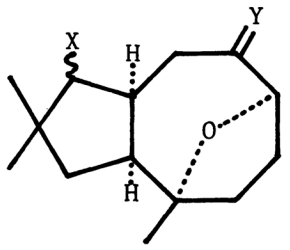
Pentalenene (2) Pentalenic acid (3) Pentalenolactone (4)

derived biosynthetically from humulene.[4,5] We should like to describe here synthesis of pentalenic acid (3).

Humulene (1) was treated with $Hg(NO_3)_2$ (3 eq, THF-H_2O (1:1), 0 °C, 1 h and then 65 °C, 3 h) [6] followed by aqueous KBr solution to give two 10α-bromomercuri-3,6-secoprotoilludane derivatives, 5[7] (31%) and 6[7] (21%) (J_{vic} of BrHg-C-H = 9 Hz in both compounds). The two mercury compounds were separately converted to two groups of corresponding 10α and 10β-hydroxy compounds, 7[7] (49%) and 8[7] (33%), and 9[7] (66%) and 10[7] (21%), respectively under Whitesides' conditions[8] (O_2, $NaBH_4$, DMF). The 7-hydroxy compounds 7 and 8 gave corresponding exomethylene compounds 9 (73%) and 10 (78%) by bromination (1. Ac_2O-Py, 2. PBr_3-ether) and dehydrobromination ($^+$AmONa, DMSO, 70 °C) and 10 was changed to 9 (75%) through oxidation (Jones Reagent) and reduction ($NaBH_4$, EtOH, 0 °C). After all 10α-hydroxy ether 9 was furnished from humulene in 34% yield. On treatment with Li (5 eq) in $EtNH_2$-THF (-78°), the ether 9 afforded cyclooctenol 11[7] in 90% yield.

Formation of the pentalenane skeleton was first attempted under the same conditions (HCO_2H, Ac_2O, rt, 24 h) as those used for the conversion of 10-deoxycyclooctenol 12[4b] to pentalenene (2) and a skeletally isomeric pentalenene derivative 18 was yielded (40%) instead of desired compound 13. Elaboration of the desired skeleton was achieved by treatment of 11 with excess $BF_3 \cdot OEt_2$ in CH_2Cl_2 at -10 °C for 30 min to give 10α-hydroxypentalenene 13[7] (20%) with other 4 compounds 14[7] (8%), 16[7] (12%), 17[7] (10%) and 19[7] (10%). 10-Deoxy compounds of 13[5], 14[4c], 16[9] and 19[4b] were previously obtained by us and the stereochemistry of 13, 14, 16 and 19 was depicted as formulae referring to the data of these deoxy compounds. On oxidation with SeO_2 (excess, EtOH-H_2O (10:1), reflux, overnight), 13 yielded an aldehyde 20[7] (72%) which was converted to methyl pentalenate (21) (68%) by treatment with MnO_2-KCN (MeOH-AcOH, catalytic amount of 18-crown ether rt, 5 days). The spectral data of 21 were completely identical with those of the natural product. Hydrolysis of 21 (MeOH-H_2O, KOH, 40 °C, 3 h) gave pentalenic acid (3) quantitatively.

Acknowledgment. We thank Dr. H. Seto for the nmr spectrum of methyl pentalenate.



5 X = α-HgBr, Y = 

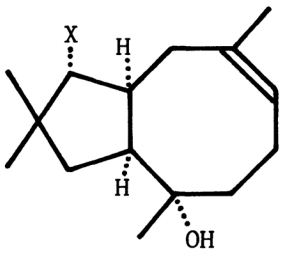
6 X = α-HgBr, Y = 

7 X = α-OH, Y = 

8 X = β-OH, Y = 

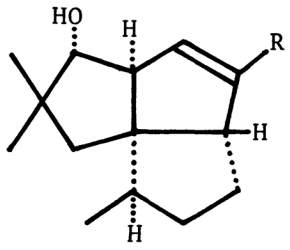
9 X = α-OH, Y = 

10 X = β-OH, Y = 



11 X = OH

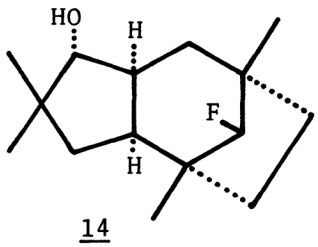
12 X = H



13 R = Me

20 R = CHO

21 R = COOMe



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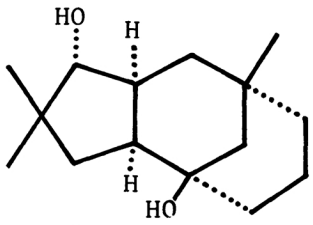

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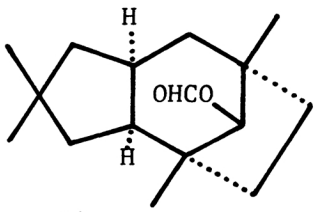

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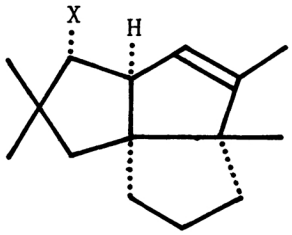
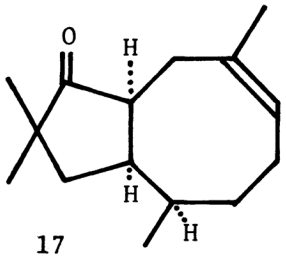


18 X = OCHO

19 X = OH



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12 $\xrightarrow[Ac_2O]{HCOOH}$ 2 and 15 -----ref. 4b

11 $\xrightarrow[Ac_2O]{HCOOH}$ 18

11 $\xrightarrow[CH_2Cl_2]{BF_3 \cdot OEt_2}$ 13, 14, 16, 17 and 19

Fig 2

References and Notes

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T. Matsumoto, ibid, 1978, 1991. d) A review: H. Shirahama, Y. Ohfune, S. Misumi, and T. Matsumoto, J. Synth. Org. Chem. Japan, 36, 569 (1978). (in Japanese).

5) Pentalenene was synthesized before isolation[3a] from natural source. Y. Ohfune, H. Shirahama, and T. Matsumoto, Tetrahedron Lett., 1976, 2869; ref. 4b.

6) Other modes of cyclization of humulene by means of Hg(II)-salt: S. Misumi, T. Ohtsuka, H. Hashimoto, Y. Ohfune, H. Shirahama, and T. Matsumoto, Tetrahedron Lett., 1979, 35.

7) Spectral data of all compounds are consistent with the structure depicted in the figure. Nmr spectra exhibited the following peaks (in $CDCl_3$ unless otherwise indicated).

5 1.18 (3H, s), 1.20 (6H, s), 1.39 (3H, s), 3.87 (1H, bd, J=6) ppm.

6 1.17, 1.21, 1.25 (each 3H, s), 4.58 (1H, d, J=6), 4.76 (2H, s).

7 0.91, 1.02, 1.19, 1.36 (each 3H, s), 3.17 (1H, d, J=7), 3.88 (1H, m).

8 0.93, 1.02, 1.20, 1.35 (each 3H, s), 3.42 (1H, d, J=3), 3.86 (1H, m).

9 0.92, 1.03, 1.22 (each 3H, s), 3.18 (1H, d, J=7), 4.57 (1H, bd, J=6), 4.73 (2H, s).

10 0.93, 1.05, 1.23 (each 3H, s), 3.49 (1H, d, J=3), 4.55 (1H, bd, J=6), 4.74 (2H, m).

11 0.94, 1.11, 1.23 (each 3H, s), 1.74 (3H, bs), 3.37 (1H, d, J=7), 5.50 (1H, t, J=6).

13 0.94 (3H, d, J=7), 0.97 (6H, s), 1.60 (3H, m), 3.33 (1H, d, J=5), 5.32 (1H, m).

14 0.92, 1.00 (each 3H, s), 1.04 (6H, s), 3.48 (1H, d, J=3.1), 3.98 (1H, d, J=53.5).

16 0.90, 0.97, 1.08 (each 3H, s), 3.34 (1H, d, J=3).

17 0.91 (3H, d, J=9.1), 0.97, 1.06 (each 3H, s), 1.58 (3H, bs), 5.41 (1H, m).

18 (CCl_4) 0.98 (9H, s), 1.59 (3H, t, J=2), 4.45 (1H, d, J=7), 5.32 (1H, bs), 7.98 (1H, s).

19 0.98 (9H, s), 1.58 (3H, t, J=2), 3.20 (1H, d, J=8), 5.39 (1H, m).

20 0.97 (3H, s), 0.98 (3H, d, J=7), 1.00 (3H, s), 3.40 (1H, d, J=5.5). 6.85 (1H, m), 9.63 (1H, s).

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