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SYNTHESIS OF PENTALENOLACTONE E AND F THROUGH BIOGENETIC LIKE CYCLIZATION OF HUMULENE

Toshikazu Ohtsuka, Haruhisa Shirahama, and Takeshi Matsumoto
Department of Chemistry, Faculty of Science,
Hokkaido University, Sapporo 060, JAPAN

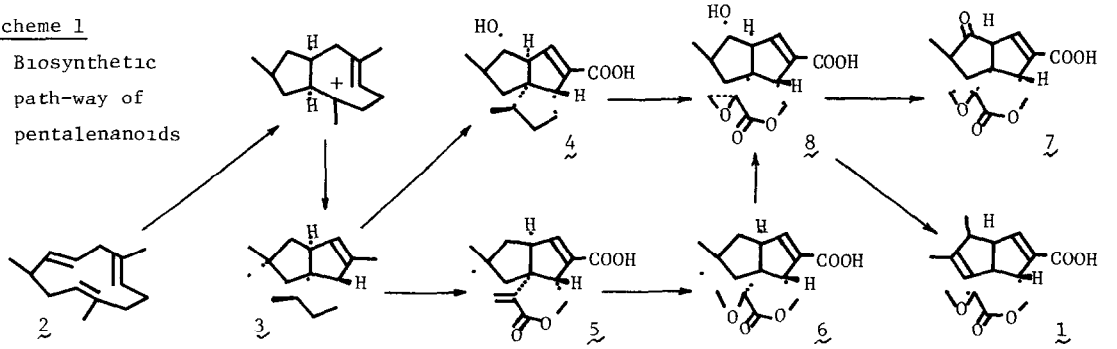
Summary 3-Methoxy-3,6-secoprotoilludan-6-one, derived from humulene, was converted to 3-pentalenen-6-ol, which furnished pentalenolactone E and F through several steps

The antibiotic properties of pentalenolactone (1)[1] served to elicit extensive investigation of its biosynthesis. The compound was demonstrated to be biosynthetically derived[2] from humulene (2) through several intermediates, pentalenene (3),[3] pentalenolactone E (5),[4] F (6),[5] G (7),[6] H (8),[7] as well as pentalenic acid (4)[7,8] (Scheme 1). The biogenetic like conversion of humulene to pentalenanoid has currently aroused interest for us.[3b,8] We should like to describe here syntheses of the pentalenolactone E (5) and F (6) from humulene (2).

Humulene (2) was previously converted to 3,6-secoprotoilludane derivatives, 9 and 10, from which pentalenene (3)[3b] and pentalenic acid (4)[8] were derived through transannular cyclizations employing HCO_2H-Ac_2O and $BF_3 \cdot OEt_2$-CH_2Cl_2 respectively as key steps. These cyclizations of 9 and 10 were initiated with elimination of water followed by generation of cation at C(2) and furnished the pentalenane skeleton which had no function on the C-ring. Since functionalization of the C-ring is necessary to reach the pentalenolactones, we took another mode of cyclization. Transformation of $\Delta^{6,7}$-double bond of a starting material into 6-keto compound was carried out in order to make cyclization initiate at C(6) (Scheme 2).

The compound 11[9] underwent hydroboration-oxidation and Jones oxidation to furnish ketones 12[10] (83 %) and its C(7) epimer 13[10] (7 %). In methanolic

Scheme 1
Biosynthetic path-way of pentalenanoids



potassium methoxide solution, 13 was brought into equilibrium with 12 (13:12= 56:36). Configuration of the C(7)-methyl groups of 12 and 13 was determined at the next stage. Transannular cyclization of 12 was achieved by treatment with formic acid at 45 °C for 2 h and then with sodium carbonate in methanol-water solution at ambient temperature for 6 h to assemble the pentalenane skelaton; 14[10] (67 %). The structure of 14 was determined by extensive ^{1}H NMR decoupling experiments in the presence of a shift reagent. The configuration of C(7)-H was alloted to α by the fact that the LIS value of C(7)-H was lager than that of C(7)-Me.

Hydroboration-oxidation of 14 gave diols 15[10] (mp 152-154 °C, 71 %) and its epimer 16[10] (mp 74-76 °C, 24 %). Since an intramolecular H-bond was observed in IR (3560 cm^{-1}, $6x10^{-4}$ mol in CCl_4), 15 was assigned to a cis-diol. Consequently, C(3)-Me was alloted to α in 15 and β in 16. Each of the diols, 15 and 16, was separately converted to the same mixture of 25 and 26 (7:1) through a series of reactions [15(16)→17(18): HCO_2H/85 °C/15 h, 17[10] (87 %), 18[10] (48 %). →19(21):SeO_2(30 mmol for 1 mmol of substrate)/EtOH/reflux/24 h, 19[10] (86 %), 21[10] (90 %). →20(22): NaCN/MnO_2/AcOH/MeOH/rt/18 h, 20[10] (80 %), 22[10] (65 %). →23(24): Jones oxd. at 0 °C, 23[10] (78 %), 24 (80 %). →25 + 26: TMSOTf/Et_3N/benzene/rt/10 min, 25 + 26 (7·1, 80 %)].

α-Methylene lactone in C-ring was assembled as follows. The mixture of 25 and 26 was brominated (NBS/THF/5 min) without separation and purification. Purification of the products on silica gel chromatography yielded bromide 27[10] (66 % from 23). Treatment of 27 with a mixture of TMSOTf, Et_3N and $NaHCO_3$ in benzene at room temperature for 24 h gave 28[10] (50 %) and 29[10] (30 %). The enone 29 was converted to 28 (TMSOTf/$(TMS)_2NH$/benzene/rt/2 h) in 80 % yield. Oxidation of 28 first with mCPBA (hexane/30 min at -15 °C and then 2 h at rt) and then with $NaIO_4$(H_2O-t-BuOH/rt/4 h) gave 30, which was subjected to reduction with $NaBH_4$(EtOH/0 °C/10 min) and then lactonization (pH 2(adjusted by 2 N HCl)/rt/2 h) to afford pentalenolactone E methyl ester (31) (31 % from 28). The synthetic ester was spectrally (^{1}H NMR and IR) identical with the ester derived from the natural product. The ester 31 was hydrolysed (1. LiOH/H_2O-THF/rt/overnight, 2. pH 2 (1 N HCl)/rt/2 h) to pentalenolactone E (5) quantitatively. The ester 31, was then oxidized (30 % H_2O_2/MeOH-H_2O/rt/24 h) to give pentalenolactone F methyl ester (32) (mp 128-130 °C, 40 %) and its epimer 33 (15 %). The spectra (^{1}H NMR, IR) of 32 were superimposable with those of the ester derived from the natural acid. The ester 32 was also hydrolysed in a similar manner as above to afford pentalenolactone F (6) (70 %).

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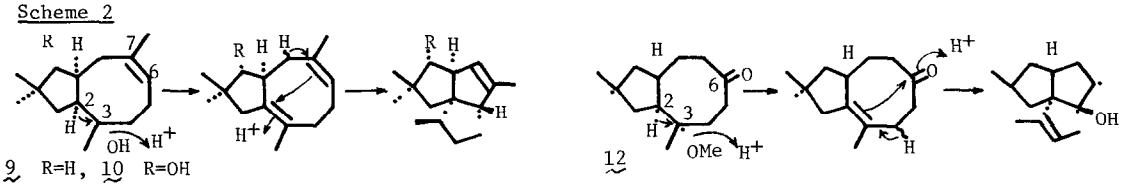
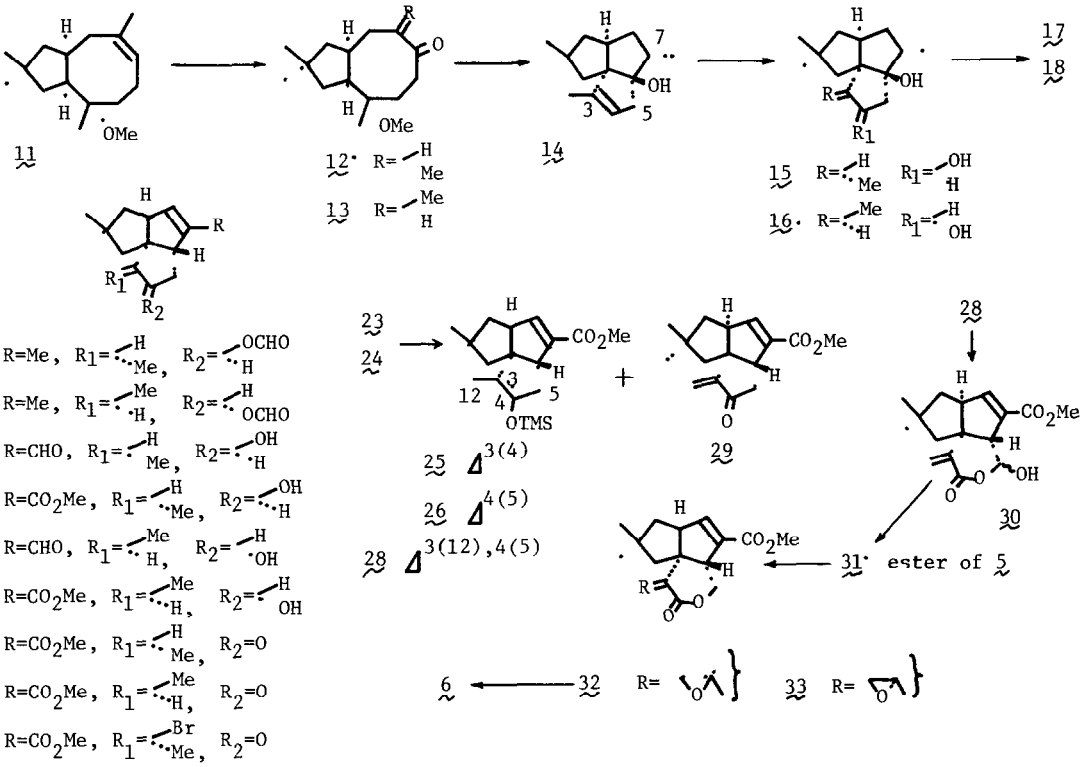
Scheme 2



9 R=H, 10 R=OH

12



of pentalenolactone E and F methyl esters and showing us the manuscript of his report (ref. 2b) before publication.

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10) Pertinent ^{1}H NMR data for all of new compounds are given below Unless otherwise stated, the NMR spectra were obtained on a 60 MHz instrument using $CDCl_3$ as solvent Spectra of pentalenolactone E and F were also described since they were not recorded in any previous report

12: δ 0.95, 1.05 (each 3H, s), 1.08 (3H, d, J=7), 1.16, 3.15 (each 3H, s).

13: δ 0 99, 1 09 (each 3H, s), 1.10 (3H, d, J=7), 1.16, 3.04 (each 3H, s)

14: δ 0.93 (3H, d, J=7), 1.05, 1 09 (each 3H, s), 1 69 (3H, bs), 1 72 (2H, s), 5 17 (1H, m)

15: δ 0.95, 0.98 (each 3H, d, J=7), 1 02, 1.06 (each 3H, s), 3.89 (1H, bq, J=3.5)

16: δ 0.97 (3H, d, J=7), 0.98, 1 05 (each 3H, s), 1 06 (3H, d, J=7), 3.80 (1H, bq, J=7).

17: δ 0 95 (3H, d, J=7), 0.97 (6H, s), 1 62 (3H, m), 1.64 (2H, s), 2.70 (1H, bd, J=9), 2.98 (1H, m), 4.62 (1H, dt, J=6.5, 9.5), 5.18 (1H, m), 8.06 (1H, s).

18: δ 0.95 (3H, d, J=7), 0 99, 1.01 (each 3H, s), 1.62 (3H, m), 1 63 (2H, s), 2.60~3.00 (2H m), 4 75 (1H, bq, J=7), 5.19 (1H, m), 8 02 (1H, s).

19: δ 0.90 (3H, s), 1 01 (3H, d, J=7), 1.01 (3H, s), 1 67 (2H, s), 3 02~3.30 (2H, m), 3.42 1H, dt, J=6.5, 9.5), 6 70 (1H, m), 9 65 (1H, s).

20: δ (CCl_4) 0.95 (3H, s), 0.96 (3H, d, J=7), 1.00 (3H, s), 1.65 (2H, s), 2.98~3.20 (2H, m), 3 33 (1H, dt, J=6 5, 9 5), 3.66 (3H, s), 6.49 (1H, m)

21: δ 0 97 (3H, s), 0.98 (3H, d, J=7), 1 02 (3H, s), 2.95~3.34 (2H, m), 3 76 (1H, bq, J=7), 6.74 (1H, m), 9 74 (1H, s).

22: δ 0.97 (3H, d, J=7), 0.99 (6H, s), 1.33, 1.78 (each 1H, d, J=14), 2 85~3 30 (2H, m), 3.70 (1H, bq, J=7), 3.71 (3H, s), 6 64 (1H, bs).

23: δ (CCl_4) 1 02 (3H, d, J=7), 1.04, 1.07 (each 3H, s), 1 87 (2H, bs), 2.90~3.30 (2H, m), 3 67 (3H, s), 6.56 (1H, m).

27: δ 1 04, 1.15, 1.70 (each 3H, s), 1.80, 2 40 (each 1H, d, J=15), 2.95 (1H, m), 3.43 (1H, t, J=2), 3.45 (1H, d, J=12), 3.72 (3H, s), 6.52 (1H, d, J=2)

28: δ 0.20 (9H, s), 1 02, 1.10 (each 3H, s), 1 86 (2H, s), 3.10 (1H, m), 3 68 (1H, m), 3.70 (3H, s), 4.72 (1H, d, J=2), 4.98 (1H, s), 5 38 (1H, m), 6.60 (1H, m)

29: δ (CCl_4) 1.08, 1.14 (each 3H, s), 2 98~3.50 (2H, m), 3.68 (3H, s), 5.28, 5 97 (each 1H, s), 6 64 (1H, m)

32: δ (100 MHz) 1.01, 1 03 (each 3H, s), 1 46 (2H, s), 2 98 (1H, d, J=5.5), 3.04(1H, d, J= 5.5), 3.45 (2H, m), 3 77 (3H, s), 4.43 (1H, dd, J=2.5, 12), 4.76 (1H, dd, J=2, 12), 6.87 (1H, bs)

33: δ (100 MHz) 1 04 (6H, s), 1 43 (1H, dd, J=6 5, 13), 1.64, 1.76, 1 85, 1.98 (2H, ABq, J= 12 5), 2 95 (1H, d, J=4 5), 3.06 (1H, d, J=4 5), 3.46~3.70 (2H, m), 3 76 (3H, s), 4 19 1H, dd, J=9, 11.5), 4.88 (1H, dd, J=6, 11.5)

5: δ (100 MHz) 1.07, 1.08 (each 3H, s), 1 47(1H, dd, J=6, 13), 1 68, 1 82, 2 11, 2.25 (2H, ABq, J=13.5), 3 19~3 45 (2H, m), 4 33 (2H, d, J=4 5), 5.59, 5 93 (each 1H, s), 7.02 (1H, t, J=2)

6: δ (100 MHz) 1 03, 1 04 (each 3H, s), 1.48 (2H, s), 3 02 (2H, s), 3 42 (2H, m), 4.44 (1H, dd, J=3, 12), 4.62 (1H, bd, J=12), 7 04 (1H, bs).

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