

IN VITRO CONVERSION OF HUMULENE TO (±)-PENTALENOLACTONE G, H,  
AND PENTALENOLACTONE

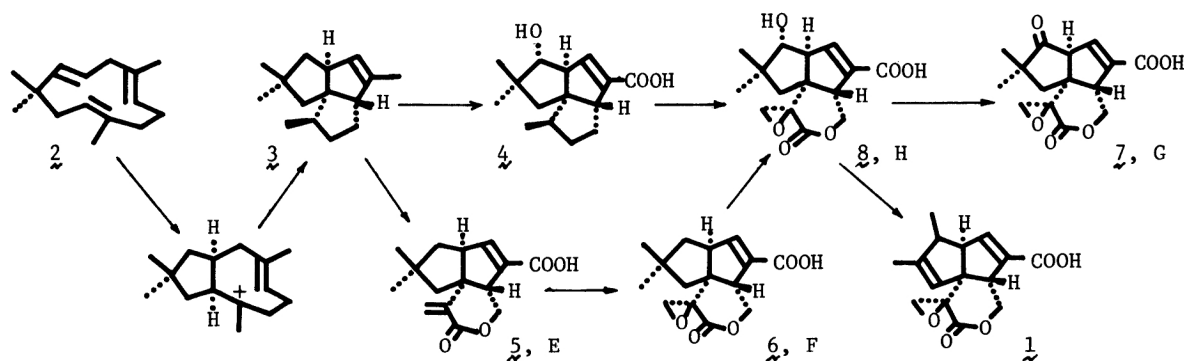
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Pentalenolactone (PL), PLH, and PLG were derived from 3,6-epoxy-3,6-seco-7(13)-protoilluden-10-ol which in turn was obtained from humulene. Conformation of PL's was studied by NMR.

Because of its antibiotic properties, the biosynthesis and chemical synthesis of pentalenolactone (1)<sup>1)</sup> has been extensively studied. The compound was shown to be biosynthetically derived from humulene (2)<sup>2)</sup> through several intermediates, pentalenene (3),<sup>3)</sup> pentalenolactone (PL) E (5),<sup>4)</sup> F (6),<sup>5)</sup> G (7),<sup>6)</sup> and H (8),<sup>7)</sup> as well as pentalenic acid (4)<sup>7)</sup> (Scheme 1). Biomimetic conversions of 2 to 3,<sup>8)</sup> 4,<sup>9)</sup> 5,<sup>10)</sup> and 6<sup>10)</sup> in racemic forms have recently been achieved in this laboratory. We should like to report here conversion of 2 to (±)-methyl esters of PLG 7, PLH 8, and PL 1.

The hydroxyether 9, obtained from humulene previously,<sup>9)</sup> was converted to 12<sup>11)</sup> (mp 59-62 °C) in 65% yield by successive treatments under the following conditions: 1) TMSCl/Et<sub>3</sub>N/CH<sub>2</sub>Cl<sub>2</sub>/15 min at 0 °C → 1 h at rt; 2) Li/EtNH<sub>2</sub>/THF/-78 °C/3 h; 3) MeI/NaH/THF/0 °C → reflux for 1 h, 4. HCl/MeOH-Et<sub>2</sub>O/0 °C/1 h; 5) BzCl/Pyr/30 min at 0 °C → 1 h at rt. The benzoate 12 was transformed to 30 through the following pathway similar to the procedure employed in the conversion<sup>10)</sup> of 10 to PLE (5).

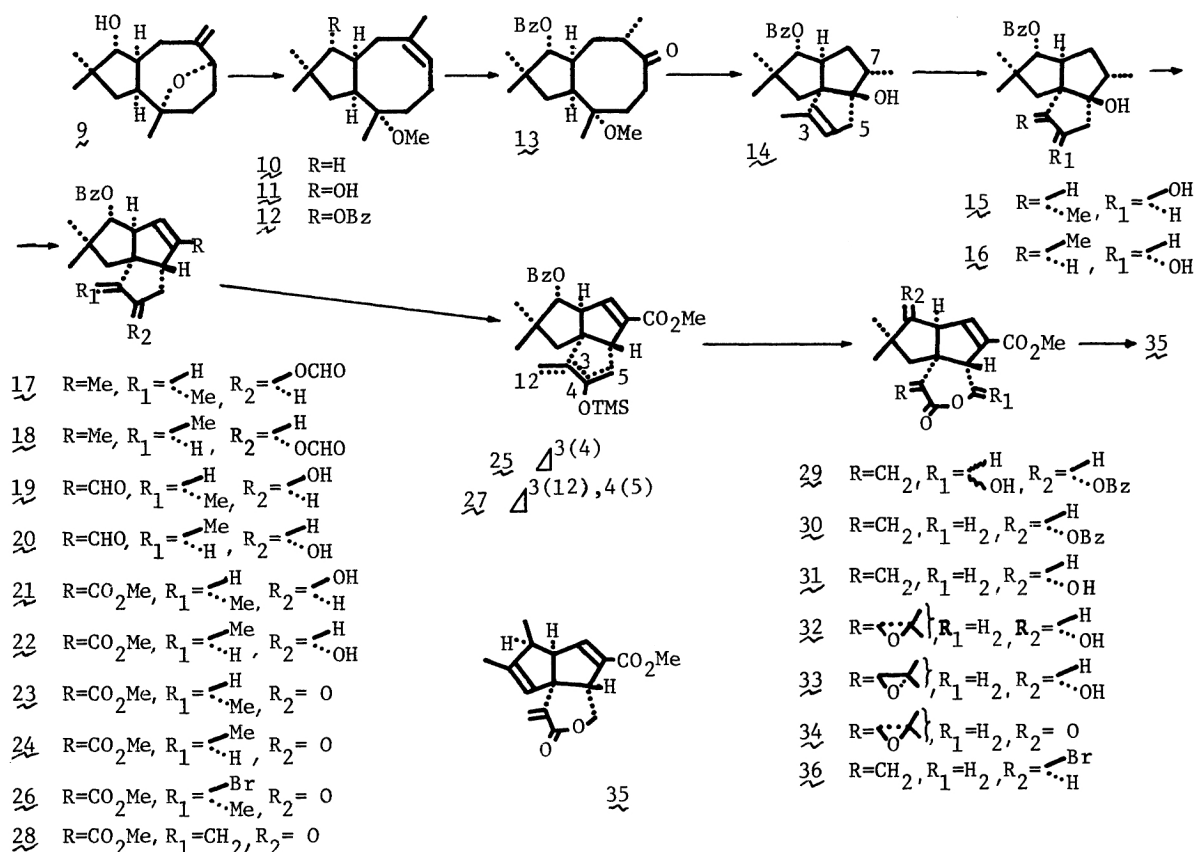
12 → 13<sup>11)</sup>: 1) B<sub>2</sub>H<sub>6</sub>/THF/0 °C/30 min; 2) H<sub>2</sub>O<sub>2</sub>/3 mol dm<sup>-3</sup>-NaOH; 3) Jones oxd. at 0 °C, mp 95-98 °C, 79%. 13 → 14<sup>11)</sup>: 1) HCO<sub>2</sub>H/45 °C/36 h; 2) Na<sub>2</sub>CO<sub>3</sub>/MeOH-H<sub>2</sub>O/rt/5 h, mp 116-118 °C, 38%. 14 → 15+16: 1) B<sub>2</sub>H<sub>6</sub>/THF/30 min at 0 °C → 1.5 h at rt; 2) H<sub>2</sub>O<sub>2</sub>/NaOH, 15<sup>11)</sup> (mp 60-62 °C, 78%) and 16<sup>11)</sup> (18%). 15(16) → 17(18): HCO<sub>2</sub>H/85 °C/48 h,



Scheme 1. Biosynthetic pathway to pentalenolactones.

17<sup>11</sup>) (mp 105-107 °C, 71%), 18<sup>11</sup>) (mp 68-70 °C, 37%). 17(18)→19(20): SeO<sub>2</sub>/EtOH/refl./48 h, 19<sup>11</sup>) (85%), 20<sup>11</sup>) (79%). 19(20)→21(22): MnO<sub>2</sub>/NaCN/AcOH/MeOH/rt/24 h, 21<sup>11</sup>) (mp 128-130 °C, 87%), 22<sup>11</sup>) (91%). 21(22)→23(24): Jones oxd. at 0 °C, 23<sup>11</sup>) (80%), 24<sup>11</sup>) (mp 124-127 °C, 78%). 23(24)→25→26<sup>11</sup>): 1) TMSOTf/Et<sub>3</sub>N/benzene/rt/10 min; 2) NBS/THF/0 °C/5 min, 60% from 23, 62% from 24. 26→27+28: TMSOTf/Et<sub>3</sub>N/NaHCO<sub>3</sub>/benzene/rt/24 h, 27<sup>11</sup>) (45%) and 28<sup>11</sup>) (33%). 28→27<sup>11</sup>): TMSOTf/(TMS)<sub>2</sub>NH/benzene/rt/2 h, 84%, 27→29→30<sup>11</sup>): 1) mCPBA/hexane/30 min at -15 °C/2 h at rt; 2) NaIO<sub>4</sub>/t-BuOH-H<sub>2</sub>O/rt/4 h; 3) NaBH<sub>4</sub>/EtOH/15 min at rt; 4) HCl/rt/2 h, 30%.

Pentalenolactone H methyl ester (32) was obtained from 30 by hydrolysis (→31) (1) LiOH/THF-H<sub>2</sub>O/55 °C/24 h; 2) HCl/rt/2 h), followed by reesterification of the carboxyl group (CH<sub>2</sub>N<sub>2</sub>/ether/0 °C), and epoxydation (1) H<sub>2</sub>O<sub>2</sub>/NaHCO<sub>3</sub>/THF-MeOH-H<sub>2</sub>O/rt/24 h; 2) HCl) in 10% yield along with 20% yield of its stereoisomer 33.<sup>11</sup>) Jones oxidation of 32 at 0 °C gave pentalenolactone G methyl ester (34). The <sup>1</sup>H NMR spectra of 32 and 34 were identical with those of esters originated from the natural products.<sup>6,7)</sup> Treatment of 31 with CBr<sub>4</sub> and PPh<sub>3</sub> in benzene at reflux temperature for 30 min afforded a properly rearranged product 35 (16%) and a bromide 36<sup>11</sup>) (70%). Since compound 35 has already been led to (+)-pentalenolactone (1) by Danishefsky et al.<sup>1b)</sup> and the <sup>1</sup>H NMR of our product coincided with the reported spectrum, the present synthesis means conversion of humulene to (+)-PL. The 1,2-shift of one methyl of the gem-dimethyl group may be operative also in biosynthesis of 1.



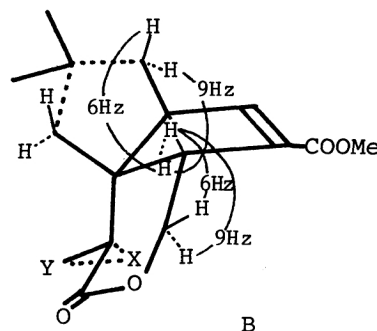
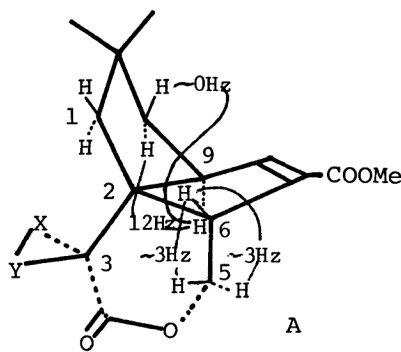
Comparison of the NMR data of PLF and PLH with those of their epimers (Table 1), in particular  $J_{5,6}$  and  $J_{9,10}$ , coupled with the well known coplanarity of lactone rings, indicated that PLF and epi-PLH (group A) took a very similar skeletal conformation approximated by A<sup>12)</sup> while epi-PLF, PLH, and PLG (group B) adopted another molecular shape expressed by B. In conformity with this assignment, signals due to H<sub>1</sub> of the group A compounds and those for H<sub>9</sub> of the group B compounds appeared at higher field than the corresponding peaks of their isomers, by the shielding effect of the oxirane ring. The NMR data of PL-Me (H<sub>5</sub>,  $\delta$  4.55, 2H, d,  $J=3.0$ ; H<sub>9</sub>, 3.35, 1H, ddd,  $J=9.0, 3.0, 2.7$ ; H<sub>10</sub>, 2.80, 1H, dqg,  $J=9.0, 7.5, 1.2$ ) and epi-PL-Me (H<sub>5a</sub>,  $\delta$  4.35, 1H, dd,  $J=12, 5$ ; H<sub>5b</sub>, 4.6, 1H, dd,  $J=12, 3$ ; H<sub>9</sub>, 3.65, 1H, m, band width 30 Hz, Ref. 1b) suggest that both compounds take a conformation similar to A. It is of interest that conformations of this class of compounds are greatly influenced by the substituent at C-10. This seems to be deserving of further study.

Table 1. <sup>1</sup>H NMR Spectra of pentalenolactones

b)	PLF-Me <sup>a)</sup> (A)		epi-PLF-Me <sup>a)</sup> (B)		PLH-Me <sup>a)</sup> (B)		epi-PLH-Me <sup>a)</sup> (A)	
	ppm	J	ppm	J	ppm	J	ppm	J
14	1.01 3H s		1.04 6H s		1.01 3H s		0.97 3H s	
15	1.03 3H s				1.03 3H s		1.04 3H s	
1	1.46 2H s		1.72 1H d	13.5	1.69 1H d	14	1.51 1H d	13
			1.90 1H d	13.5	2.07 1H d	14	1.74 1H d	13
10	1.53 1H d	12	1.44 1H dd	13, 6	3.56 1H d	6	3.61 1H s	
	1.71 1H t	12	1.74 1H dd	13, 9				
12	3.00 1H d	5	2.95 1H d	4.5	2.96 1H d	4.5	3.13 1H d	5
	3.02 1H d	5	3.06 1H d	4.5	3.08 1H d	4.5	3.22 1H d	5
9			2.98 1H ddt	9, 6, 3	2.83 1H dt	6, 3	3.29 1H t	3
6	3.43 2H m		3.57 1H ddt	9, 6, 3	3.52 1H ddt	9, 6, 3	3.44 1H tt	3.5, 3
7 <sup>+</sup>	3.77 3H s		3.76 3H s		3.77 3H s		3.78 3H s	
5	4.43 1H dd	12, 3	4.19 1H dd	11.5, 9	4.18 1H dd	12, 9	4.50 1H dd	12, 3.5
	4.76 1H dd	12, 2	4.88 1H dd	11.5, 6	4.89 1H dd	12, 6	4.72 1H dd	12, 3.5
8	6.87 1H bs		6.87 1H t	2	6.99 1H t	2.5	6.95 1H t	3

b)	PLG-Me <sup>6)</sup> (B)	
	ppm	J
14	1.12 3H s	
15	1.15 3H s	
1	2.06 1H d	14.3
	2.24 1H d	14.3
12	2.97 1H d	4.5
	3.14 1H d	4.5
9	3.19 1H t	3.0
6	3.72 1H dddd	9.7, 6.0, 3.0, 2.0
7 <sup>+</sup>	3.76 3H s	
5	4.21 1H dd	11.5, 9.7
	4.96 1H dd	11.5, 6.0
8	6.85 1H dd	3.0, 2.0



a) Measured by a JEOL JNM GX-500 instrument. Another spectrum was taken by a 100 MHz equipment.  
 b) Assignment. 7<sup>+</sup> represents an ester methyl group.

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- 11) Satisfactory spectral data were obtained for all new compounds. Mp's were given for crystalline compounds and  $^1\text{H}$  NMR data for important compounds are recorded below. The data were obtained by 100 MHz (a) and 60 MHz (b) instruments in  $\text{CDCl}_3$  soln unless otherwise stated.  
13:  $\delta$  (b,  $\text{CCl}_4$ ) 1.03 (3H, d,  $J=7$ ), 1.07 (6H, s), 1.19, 3.13 (each 3H, s), 5.05 (1H, d,  $J=9$ ).  
14:  $\delta$  (b) 1.03 (3H, d,  $J=7$ ), 1.10, 1.18 (each 3H, s), 1.78 (3H, bs), 5.11 (1H, d,  $J=10$ ), 5.27 (1H, m).  
27:  $\delta$  (b) 0.20 (9H, s), 1.12, 1.15 (each 3H, s), 4.90 (1H, m), 4.98 (1H, m), 5.03 (1H, bs), 5.40 (1H, m), 6.75 (1H, m).  
30:  $\delta$  (a) 1.13, 1.15 (each 3H, s), 1.91, 2.41 (each 1H, d,  $J=14$ ), 3.77 (3H, s), 4.24 (1H, dd,  $J=5, 11.5$ ), 4.40 (1H, dd,  $J=4, 11.5$ ), 4.93 (1H, d,  $J=4$ ), 5.66, 5.95 (each 1H, s), 7.08 (1H, bs).  
33:  $\delta$  (a) 0.97, 1.04 (each 3H, s), 1.51, 1.74 (each 1H, d,  $J=13.5$ ), 3.13, 3.22 (each 1H, d,  $J=5$ ). 3.30 (1H, m), 3.44 (1H, m), 3.60 (1H, bs), 3.78 (3H, s), 4.50 (1H, dd,  $J=3.5, 12$ ), 4.72 (1H, dd,  $J=3.5, 12$ ), 6.95 (1H, t,  $J=2.5$ ).  
36:  $\delta$  (a) 1.08, 1.11 (each 3H, s), 2.08 (2H, s), 3.78 (3H, s), 4.07 (1H, d,  $J=8.5$ ), 4.25 (1H, dd,  $J=6, 12$ ), 4.40 (1H, dd,  $J=4.5, 12$ ), 5.57, 6.01 (each 1H, s), 7.02 (1H, t,  $H=2.5$ ).  
12) A quite similar endo-lactone conformation has been found for a PL derivative by X-ray analysis (Ref. 1a).

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