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

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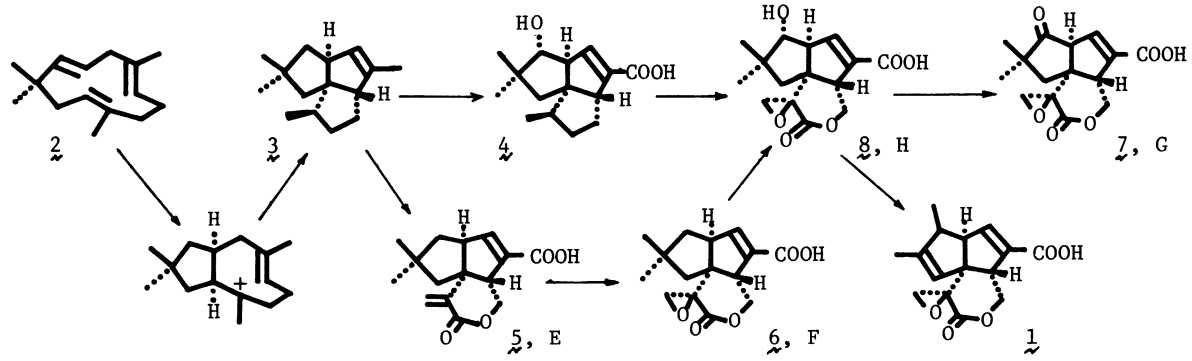
Pentalenolactone (PL), PLH, and PLG were derived from 3,6-epoxy -3,6-seco-7(13)-protoilluden-10-ol which in turn was obtained from humulene. Conformation of PL's was studied by NMR.

Because of its antibiotic properties, the biosynthesis and chemical synthesis of pentalenolactone (1)[1] has been extensively studied. The compound was shown to be biosynthetically derived from humulene (2)[2] through several intermediates, pentalenene (3),[3] pentalenolactone (PL) E (5),[4] F (6),[5] G (7),[6] and H (8),[7] as well as pentalenic acid (4)[7](Scheme 1). Biomimetic conversions of 2 to 3,[8] 4,[9] 5,[10] and 6[10] 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,[9] was converted to 12[11] (mp 59-62°C) in 65% yield by successive treatments under the following conditions: 1) $TMSCl/Et_3N/CH_2Cl_2$/15 min at 0 °C→1 h at rt; 2) $Li/EtNH_2/THF$/-78 °C/3 h; 3) MeI/NaH/THF/0 °C→reflux for 1 h, 4. $HCl/MeOH\text{-}Et_2O$/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[10] of 10 to PLE (5).

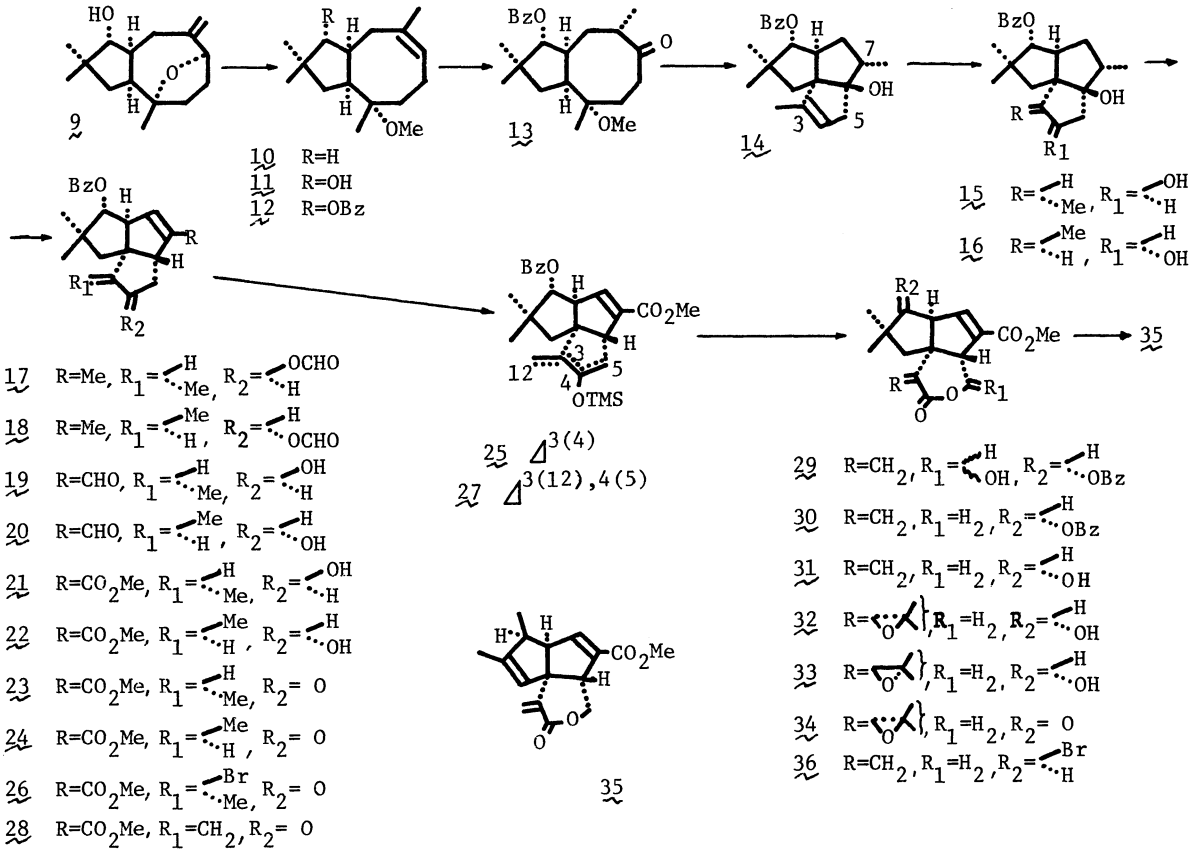
12→13[11]: 1) B_2H_6/THF/0 °C/30 min; 2) H_2O_2/3 mol dm^{-3}-NaOH; 3) Jones oxd. at 0 °C, mp 95-98 °C, 79%. 13→14[11]: 1) HCO_2H/45 °C/36 h; 2) $Na_2CO_3/MeOH\text{-}H_2O$/rt/5 h, mp 116-118 °C, 38%. 14→15+16: 1) B_2H_6/THF/30 min at 0 °C→1.5 h at rt; 2) H_2O_2/NaOH, 15[11] (mp 60-62 °C, 78%) and 16[11](18%). 15(16)→17(18): HCO_2H/85 °C/48 h,



Scheme 1. Biosynthetic pathway to pentalenanoids.

17[11] (mp 105-107 °C, 71%), 18[11] (mp 68-70 °C, 37%). 17(18)→19(20): SeO_2/EtOH /refl./48 h, 19[11] (85%), 20[11] (79%). 19(20)→21(22): MnO_2/NaCN/AcOH/MeOH/rt/24 h, 21[11] (mp 128-130 °C, 87%), 22[11] (91%). 21(22)→23(24): Jones oxd. at 0 °C, 23[11] (80%), 24[11] (mp 124-127 °C, 78%). 23(24)→25→26[11]: 1) TMSOTf/Et_3N/ benzene/rt/10 min; 2) NBS/THF/0 °C/5 min, 60% from 23, 62% from 24. 26→27+28: TMSOTf/Et_3N/$NaHCO_3$/benzene/rt/24 h, 27[11] (45%) and 28[11] (33%). 28→27[11]: TMSOTf /$(TMS)_2NH$/benzene/rt/2 h, 84%, 27→29→30[11]: 1) mCPBA/hexane/30 min at -15 °C/2 h at rt; 2) $NaIO_4$/t-BuOH-H_2O/rt/4 h; 3) $NaBH_4$/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_2O/55 °C/24 h; 2) HCl/rt/2 h), followed by reesterification of the carboxyl group (CH_2N_2/ether/0 °C), and epoxydation (1) H_2O_2/$NaHCO_3$/THF-MeOH-H_2O/rt/24 h; 2) HCl) in 10% yield along with 20% yield of its stereoisomer 33.[11] Jones oxidation of 32 at 0 °C gave pentalenolactone G methyl ester (34). The ^1H NMR spectra of 32 and 34 were identical with those of esters originated from the natural products.[6,7] Treatment of 31 with CBr_4 and PPh_3 in benzene at reflux temperature for 30 min afforded a properly rearranged product 35 (16%) and a bromide 36[11] (70%). Since compound 35 has already been led to (±)-pentalenolactone (1) by Danishefsky et al.[1b] and the ^1H 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.

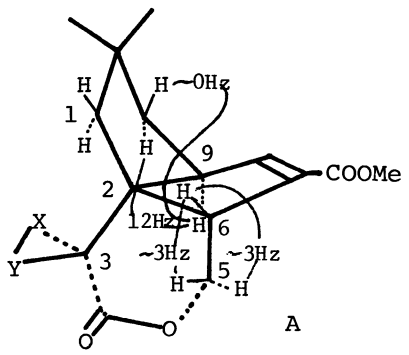


Comparison of the NMR data of PLF and PLH with those of their epimers (Table 1), in particular $J_{5,6}$ and $J_{9,10}$, coupled with the well known coplanarity of lactone rings, indicated that PLF and epi-PLH (group A) took a very similar skeletal conformation approximated by A[12] while epi-PLF, PLH, and PLG (group B) adopted another molecular shape expressed by B. In conformity with this assignment, signals due to H_1 of the group A compounds and those for H_9 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_5, δ 4.55, 2H, d, J=3.0; H_9, 3.35, 1H, ddd, J=9.0, 3.0, 2.7; H_{10}, 2.80, 1H, dqq, J=9.0, 7.5. 1.2) and epi-PL-Me (H_{5a}, δ 4.35, 1H, dd, J=12, 5; H_{5b}, 4.6, 1H, dd, J=12, 3; H_9, 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.

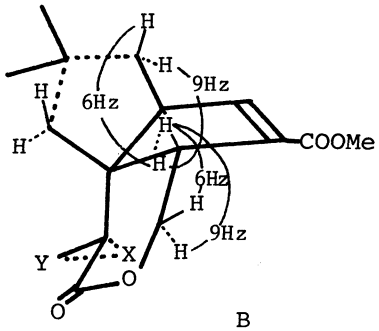
Table 1. ^{1}H NMR Spectra of pentalenolactones

b)	PLF-Me[a] (A) ppm	J	epi-PLF-Me[a] (B) ppm	J	PLH-Me[a] (B) ppm	J	epi-PLH-Me[a] (A) 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	3.43 2H m		2.98 1H ddt	9, 6, 3	2.83 1H dt	6, 3	3.29 1H t	3
6			3.57 1H ddt	9, 6, 3	3.52 1H ddt	9, 6, 3	3.44 1H tt	3.5, 3
7+	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[6] (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+	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



B

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

We thank Dr. Seto (Tokyo Univ.) for the ^{1}H NMR spectra of pentalenolactone G and H and Prof. Danishefsky (Yale Univ.) for the ^{1}H spectrum of compound 34.

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11) Satisfactory spectral data were obtained for all new compounds. Mp's were given for crystalline compounds and ^{1}H NMR data for important compounds are recorded below. The data were obtained by 100 MHz (a) and 60 MHz (b) instruments in $CDCl_3$ soln unless otherwise stated.

13: δ (b, 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: δ (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: δ (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: δ (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: δ (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: δ (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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