Nous avons inoculé intrapéritonéalement 10^6 cellules de leucémie, souche L 1210, à 6 souris pour chaque groupe——souche BDF_1 ($C_{57}BL/6♀ \times DBA/2♂$), femelles qui sont agées de 6—7 semaines.

Le traitement a été commencé 24 hr après l'inoculation de cellules de leucémie, et continué pendant 5 jours, une fois par jour.

Les substances ont été dissoutes dans une solution saline physiologique.

Pour le témoin, nous avons injecté la même volume de solution saline à la souris.

Les résultats sont présenté dans le tableau II.

En résumant nos résultats, le dihydronivalenol est presque aussi puissant que le nivalenol quant à l'inhibition de la synthèse des protéines des réticulocytes, et plus effectif que le nivalenol sur l'activité antileucémique, mais la toxicité aiguë du dihydronivalenol est moins grande que celle du nivalenol.

Nous voulons maintenant continuer nos recherches dans le but de mettre au point le dihydronivalenol comme medicament nouveau contre la leucemie.

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A Total Synthesis of a *dl*-Prostaglandin B_1

The prostaglandins, a family of C_{20} prostanoic acids and biologically highly active substances having diverse pharmacological properties, have received considerable attention.[1] Recently, total syntheses of prostaglandin B_1,[2,3] $F_{1\alpha}$,[3] and E_1[4] have been reported. Now we wish to report the total synthesis of the racemic prostaglandin B_1 in fairly short steps.

The keto acid (1) was prepared according to a slightly modified Bowman's method:[5] triethyl ethane-1,1,2-tricarboxylate[6] was transesterified to the tribenzyl ester with sodium ethoxide as catalyst, and the sodium salt of tribenzyl ester was condensed with the half acid chloride of monoethyl azelaate in refluxing benzene to give the tribenzyl oxoester. Catalytic hydrogenolysis of this ester over 10% Pd-$SrCO_3$ in ethyl acetate afforded the corresponding oxo tricarboxylic acid and finally decarboxylation of the acid in refluxing ethyl acetate resulted

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4) E.J. Corey, N.H. Andersen, R.M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R.E.K. Winter, *J. Am. Chem. Soc.*, **90**, 3245 (1968); E.J. Corey, I. Vlattas, N.H. Andersen, and K. Haeding, *ibid.*, **90**, 3247 (1968).
5) R.E. Bowman, *J. Chem. Soc.*, **1950**, 325.
6) G.S. Fonken and W.S. Johnson, *J. Am. Chem. Soc.*, **74**, 832 (1952).

in the β-oxo acid (**1**) (over all yield 27%), mp 76—78°,[7] [IR ν_{max}^{Nujol} cm^{-1}: 3750, 3300, 1724, 1698].

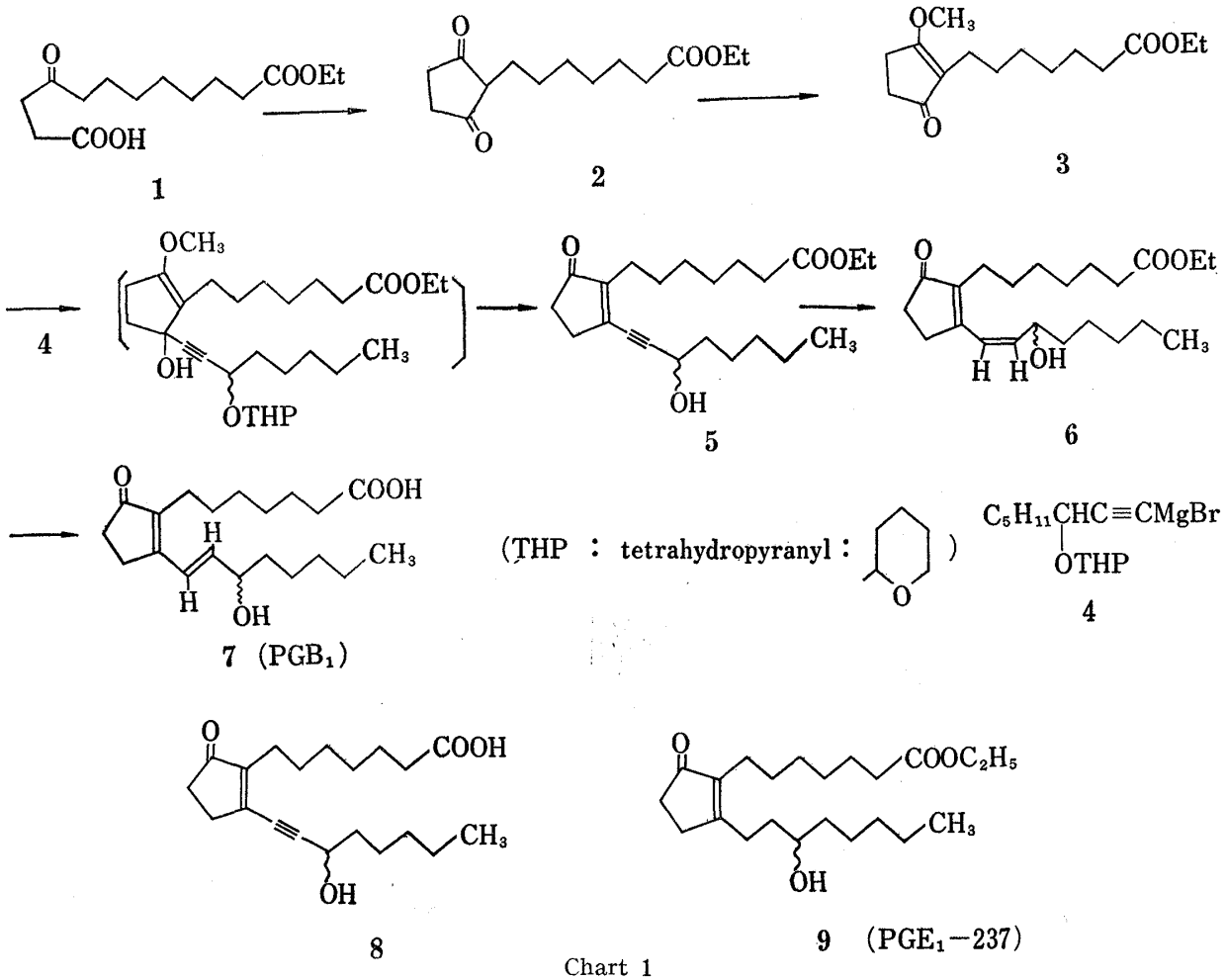

Chart 1

Cyclization [8] of the β-oxo acid (**1**) to a cyclopentane-1,3-dione derivative (**2**) was carried out in the presence of $AlCl_3$ and propionyl chloride in nitrobenzene at 80° for 3.5 hr (in 63.3% yield) accompanied by a small amount of free acid, mp 150—153°. The dione (2), mp 94—95°, was characterized by the following physical properties; [UV λ_{max}^{EtOH} mμ (ε): 250 (16500), 270 (5700; shoulder); IR ν_{max}^{Nujol} cm^{-1}: 2500 (enol OH), 1887, 1739; and NMR:[9] 1.18 (3H, t), 4.04 (2H, q), 2.33 (4H, s), 10.12 (H, s; enol OH)]. Treatment of **2** with diazomethane in ether gave the methyl enol ether (**3**), in 85.4% yield, [bp 163—165° (0.04 mmHg)[7] (bath temp.), UV λ_{max}^{EtOH} mμ (ε): 252 (18100); IR ν_{max}^{liq} cm^{-1}: 1749, 1695, 1637; NMR: 1.25 (3H, t), 4.14 (2H, q), 3.96 (3H, s)].

Grignard reaction [10] of **3** with an acetylenic magnesium bromide (**4**) in ether–tetrahydrofuran mixture (1:1) under reflux in nitrogen atmosphere followed by treatment with a dilute mineral acid at room temperature for 20 hr produced, after chromatography on silica gel using benzene–chloroform for elution, pure acetylenic ester (**5**), in 14% yield, as a oily substance [UV λ_{max}^{EtOH} mμ (ε); 272 (18700); IR ν_{max}^{liq} cm^{-1}: 3344, 2232, 1733, 1695, 1613; NMR: 0.39 (3H, t;

7) All melting and boiling points are uncorrected. Satisfactory elemental analyses were obtained for all compounds unless otherwise noted.
8) For this procedure, see H. Schick, G. Lehmann, and G. Hilgetag, *Chem. Ber.*, **100**, 2973 (1967).
9) The NMR spectra were measured using Varian A-60 spectrometer and the chemical shifts are expressed in ppm units from the internal standard of tetramethylsilane in $CDCl_3$ solution.
10) This reaction was carried out by means of the very slow inverse addition of the Grignard solution in order to avoid attack of the ester group of **3** by the Grignard reagent.

CH_3), 1.26 (3H, t), 4.16 (2H, q), 4.68 (1H, t, C<u>H</u>–OH)]. Alkaline hydrolysis of **5** to the acetylenic acid (**8**) was unsuccessful but instead decomposition occurred.

Selective hydrogenation of **5** in the presence of Lindlar's catalyst[11] with a small amount of quinoline in benzene gave after chromatography (silica gel, benzene–chloroform) a *cis*–olefinic ester (**6**), in 96% yield [UV λ_{max}^{EtOH} mμ (ε): 278 (20800), IR ν_{max}^{liq} cm^{-1}: 3350, 1739, 1695, 1634]. The NMR spectrum of **6** exhibited signals at 1.26 (3H, t) and 4.15 (2H, q) due to the ethyl ester, and 6.50 (1H, d, J=12.0 cps) and 5.87 (1H, dd, J=12.0 and J=9.5 cps) assigned to the *cis*–vinyl proton. The *cis*–olefinic ester (**6**) was subjected to prolonged catalytic hydrogenation in the presence of a large amount of Lindlar's catalyst to produce the ethyl ester of PGE_1-237 (**9**), in quant. yield, UV λ_{max}^{EtOH} mμ (ε): 237 (13700).

Treatment of 6 with 10% KOH in 50% methanol at 50° for 10 hr followed by acidification afforded a oily acidic substane, which after carefully repeated silica gel column chromatography using chloroform–ethyl acetate for elution furnished pure *dl*–prostaglandin B_1 (**7**) in waxy state in 96% yield; [UV λ_{max}^{EtOH} mμ (ε): 278 (26400); IR ν_{max}^{liq} cm^{-1}: 970 1595, 1640, 1670, 1725, 3300; NMR: 6.85 (1H, d, J=16.0 cps), 6.25 (1H, dd, J=16.0 cps and J=5.5 cps), 6.15 (OH, COOH broading singlet), 4.36 (1H, m, -C<u>H</u>-OH)]. The mass spectral analysis of **7** reveaedl the typical fragmentation pattern observed in the spectra of natural prostagrandins.[12]

Table I. The Mass Spectrum of Prostaglandin B_1

m/e	% of base peak	
189	7.5	$M^+-(C_6H_{12}COOH+H_2O)$
191	9.5	
217	8.2	
219	100.0	$M^+-(C_5H_{11}+CO+H_2O)$
220	21.8	$M^+-(C_5H_{11}+COOH)$
235	22.4	
237	29.2	$M^+-(C_5H_{11}+CO)$
238	6.1	
247	20.4	$M^+-(C_5H_{11}+H_2O)$
265	2.7	$M^+-(C_5H_{11})$
289	10.2	
290	3.4	$M^+-(H_2O+CO)$
318	7.5	$M^+-(H_2O)$
336	38.8	(Parent)
337	9.5	(P+1)
338	4.8	(P+2)

Isotope Abandances

m/e	% of P
336(P)	100
337(P+1)	24.6
338(P+2)	8.7

Calcd. % of (P+1) : 22.3

In Table 1 are listed some of the typical fragments in the mass spectrum of **7**. The spectrum showed a parent ion at *m/e* 336. The base peak (M^+-117) is formed by splitting off $C_6H_{12}O_2$ ($C_5H_{11}+CO+H_2O$). Moreover, the spectrum exhibited peaks resulting from the loss of the fragment 71 (C_5H_{11}) and due to loss of the fragments 89 ($C_5H_{11}+H_2O$), 99 ($C_5H_{11}+CO$), and 116 ($C_5H_{11}+COOH$). The peak at 189 is formed by splitting off $C_7H_{15}O_3$($C_6H_{12}COOH+H_2O$).

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