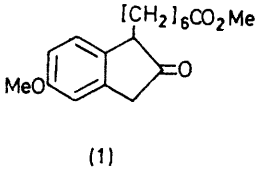
A Stereoselective Total Synthesis of Prostaglandin E_1

By D. TAUB, R. D. HOFFSOMMER, C. H. KUO, H. L. SLATES, Z. S. ZELAWSKI, and N. L. WENDLER*

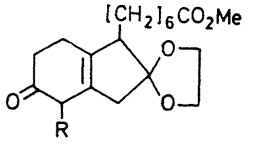
(*Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey* 07065)

Summary A total synthesis of prostaglandin E_1 incorporating stereochemical control at the nuclear chiral centres is presented.

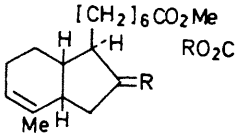
WE report a synthesis of prostaglandin E_1 (**8**) which incorporates a high degree of stereoselectivity in the generation of the nuclear asymmetric centres and good to excellent yields at the various stages.[1]



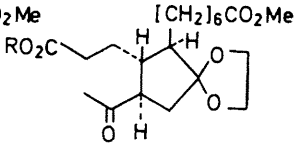
(1)



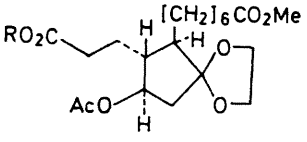
(2) R=H
(2a)R=Me



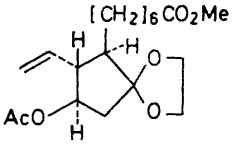
(3) R=O
(3a)R=



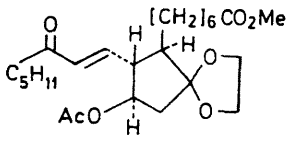
(4) R=H
(4a)R=PhCH$_2$



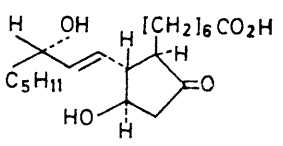
(5) R=PhCH$_2$
(5a)R=H



(6)



(7)



(8)

Stereochemical control was achieved through construction of a *cis*-hydrindanone system in which a thermodynamically predominant (5 : 1) *exo*-side-chain orientation prevails (*cf.* **3**). Final *trans–trans*-stereochemical disposition about the nuclear asymmetric centres was accomplished *via* unidirectional epimerization subsequent to oxidative scission (**3a** → **4**).

Conversion of 6-methoxy-3-indanol[2] into triphenyl-6-methoxy-3-indanylphosphonium bromide (Ph_3P·HBr, CH_2Cl_2, 25°) followed by Wittig coupling with methyl 6-formylheptanoate[3] ($KOBu^t$, Me_2SO) and subsequent isomerization (CF_3CO_2H, $CHCl_3$, 15°) produced methyl 6-methoxy-3-indeneheptanoate (m.p. 30—31·5°). Hydroxylation of the latter (OsO_4, Py) followed by rearrangement (toluene-*p*-sulphonic acid, C_6H_6, 25°) afforded (**1**) m.p. 33·5—35°. Successive acetalization [$(CH_2OH)_2$, C_6H_6, toluene-*p*-sulphonic acid], saponification (KOH, MeOH, 25°), and Birch reduction of the free acid (Li, NH_3) followed by esterification (CH_2N_2) and hydrolysis (50% aq. HOAc, THF, 10°) afforded (**2**). Methylation of (**2**) (Ph_3CLi, MeI, hexamethylphosphoramide–THF) yielded exclusively (**2a**; R = Me); n.m.r. (C_6D_6) δ 1·07 (3H, d, *J* 7 Hz). Compound (**2a**) was successively reduced [$LiAlH(OBu^t)_3$, THF, 0°], deacetalized (1·5N-aq. $HClO_4$, THF, 0°), and isomerized (NaOMe, MeOH) to the corresponding $\Delta^{1(7a)}$-ketone [λ_{max} (MeOH) 239 nm (ε 13,500)], and the latter was hydrogenated (10% Pd/C, MeOH) to give, after chromatography on silica, methyl *cis*-6-hydroxy-7-methyl-2-oxo-3-hydrindaneheptanoate. Mesylation of the latter ($MeSO_2Cl$, Py, 0°) followed by elimination (Me_2SO, 100°, 7 hr.) produced (**3**), which was purified by chromatography on silica; *M* 292 (mass spec.); n.m.r. ($CDCl_3$) δ 1·67 (3H, t, *J* 1·5 Hz) and 5·50 (1H, m). Oxidation ($KMnO_4$–$NaIO_4$) of (**3**) as its acetal derivative (**3a**) (*S*-benzylisothiuronium salt of free acid: m.p. 139—141°) followed by epimerization of the acetyl function (NaOMe, MeOH, 25°) yielded the seco-acid (**4**), which was converted into its benzyl ester ($PhCHN_2$) (**4a**) Baeyer–Villiger oxidation of which (CF_3CO_3H, Na_2HPO_4, CH_2Cl_2) gave (**5**). Hydrogenolysis (Pd/C–EtOAc) of (**5**) to (**5a**), followed by oxidative decarboxylation [$Pb(OAc)_4$, Cu^{2+}, Py–C_6H_6, *hν*][4] yielded olefin (**6**) [i.r. (neat) 5·75, 6·10, 10·50, and 10·85 μm; n.m.r. ($CDCl_3$) δ 6·0—4·68 (4H, m)]. Oxidation of (**6**) (OsO_4–$NaIO_4$) followed by Wittig coupling with dimethyl 2-oxoheptylphosphonate[5] (NaH, THF) yielded the derivative (**7**)

of (±)-15 dehydroprostaglandin E_1, λ_{max} (MeOH) 228 nm (ε 14,000); i.r. ($CHCl_3$) 5·78, 5·90 (infl.), 6.00, 6·17, and 10·55 μm.

Reduction of (7) ($NaBH_4$, MeOH, 0°) followed by saponification (KOH, MeOH, 25°, 3 hr.) of the more polar C-15-epimer yielded (±)-prostaglandin E_1 cyclic ethylene acetal, m.p. 81—83°. Hydrolysis of the latter (50% aq. HOAc, 25°, 3 hr.) afforded directly crystalline (±)-prostaglandin E_1 (8), m.p. 112—113°, identical in its i.r., n.m.r., mass spectrum† (methyl ester), and t.l.c. behaviour with natural (−)-prostaglandin E_1.‡ The synthetic (±)-material exhibited one-half the biological activity of (−)-prostaglandin E_1 in the cyclic AMP assay.[6]

(*Received, July 20th*, 1970; *Com.* 1175.)

† Kindly determined by Dr. George Albers-Schonberg of these laboratories.
‡ Kindly supplied by Dr. J. E. Pike of the Upjohn Co. through the good offices of Dr. Max Tishler.

[1] For other syntheses of prostaglandin E_1 by groups at Harvard University (a) and the Upjohn Co. (b) respectively, see: (a) E. J. Corey, N. H. Anderson, R. M. Carlson, J. Paust, E. Vedejs, I. Vlattas, and R. E. K. Winter, *J. Amer. Chem. Soc.*, 1968, **90**, 3245; E. J. Corey, I. Vlattas, N. H. Anderson, and K. Harding, *ibid.*, p. 3247; E. J. Corey, R. Noyori, and T. K. Schaaf, *ibid.*, 1970, **92**, 2586. (b) W. P. Schneider, U. Axen, F. H. Lincoln, J. E. Pike, and J. L. Thompson, *ibid.*, 1968, **90**, 5894; U. Axen, F. A. Lincoln, and J. L. Thompson, *Chem. Comm.*, 1969, 303.
[2] J. Sam and T. C. Snapp, *J. Pharm. Sci.*, 1965, **54**, 756.
[3] W. M. McLamore, W. D. Celmer, J. V. Bogert, F. C. Pennington, B. A. Sobin, and I. A. Solomons, *J. Amer. Chem. Soc.*, 1953, **75**, 105.
[4] J. D. Bacha and J. K. Kochi, *Tetrahedron*, 1968, **24**, 2215.
[5] E. J. Corey, N. M. Weinschenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675.
[6] F. A. Kuehl, jun., J. L. Humes, J. Tarnoff, V. J. Cirillo, and E. A. Ham, *Science*, 1970, **169**, 883.