A New Stereoselective Total Synthesis of Prostaglandin E_1 and its Optical Antipodes

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Summary An effective total synthesis of prostaglandin E_1 with optical resolution of the initial intermediate and an efficient new route to the key intermediate (**5a**) is described.

THE Diels–Alder] derived from *trans*-piperylene and maleic anhydride]ubmitted to methanolysis (1 mol. equiv. NaOMe–MeOH/0°) to give the 1-monomethyl ester (±)-(**1**), m.p. 110—112°.†‡ Resolution of (**1**) *via* its dehydroabietylammonium (daa) salt (80%), m.p. 163—165°, yielded (−)-(**1**) (natural series), m.p. 60—61°, $[\alpha]_D$ ($CHCl_3$) −69° {daa salt, m.p. 143—145°, yielded (+)-(**1**) m.p. 60—63°, $[\alpha]_D$ ($CHCl_3$) +67·7°}. Homologation of (**1**) by established procedure[2] gave diacid (±)-(**2**) (70%), m.p. 148—150°; (−)-(**2**), m.p. 98·5—100°, $[\alpha]_D$ ($CHCl_3$) −55·6°. Iodolactonization[3] of (**2**) yielded *exclusively* (±)-(**3**), (98%), m.p. 150—152°; (−)-(**3**) m.p. 170° (decomp.), $[\alpha]_D$ ($CHCl_3$) −3°, which was reduced[4] as its methyl ester to lactonic ester (±)-(**3a**) (95%), m.p. 83–84°. The corresponding acid (±)-(**3b**) had m.p. 138—140°; (−)-(**3b**) m.p. 118—120·5°, $[\alpha]_D$ $(CHCl)_3$ −54·7° [independently (**3b**) was resolvable *via* its daa salts into (+)- and (−)-(**3b**)]. Saponification of (**3a**) followed by dehydration of the corresponding dimethyl ester afforded (**4**) (90%). The corresponding diacid (±)-(**4a**) had m.p. 121—122·5°; (−)-(**4a**), m.p. 102·5—104°, $[\alpha]_D$ ($CHCl_3$) −99·6°. The diester (**4**) underwent cyclization *unidirectionally* with ensuing alkylation to give (**5**); the latter was converted directly [(i) collidine–LiI, 170°; (ii) CH_2N_2] into (**5a**) [80—85% from (**4**)], which was identical with material synthesized by another route.[5]

Transformation of (**5a**) into (**6**) was effected *via* the ethylene acetal derivative[5] (40—45%) δ ($CDCl_3$) 3·68 (6H, s, 2 OMe) and 3·90br (5H, s, $-OCH_2CH_2O-$ and *H*–COH) p.p.m.; $[\alpha]_D$ ($CHCl_3$) +14·7°. Lactonization of (**6**) gave (**7**) which yielded (NaH, HCO_2Me/25°) (±)-(**7a**) (75%), m.p. 88—90°; λ_{max} (MeOH) 252 nm (ε 9550); λ_{max} (MeOH/OH⁻ 286 nm (ε 16,800); (**7a**), m.p. 80—81°. Ozonolysis of (**7a**) with concluding acetylation afforded (±)-(**8**) (40—45%) m.p. 82—84°; λ_{max} MeOH 229 nm (ε 9100); (**8**) $[\alpha]_D$ ($CHCl_3$) +30°. Olefinic bond cleavage of (**8**) (OsO_4–$NaIO_4$–MeOH) gave an intermediate methoxalyl aldehyde, which on Wittig coupling and deoxalylation yielded (**9**), a derivative of 15-dehydroprostaglandin E_1 [55% from (**8**)]; λ_{max} (MeOH) 232 nm (ε 12,300); δ ($CDCl_3$) 0·83 (3H, t, *J* 6 Hz), 6·17 (14-H, d, *J* 16 Hz), and 6·73 (13-H, dd, *J* 16 and 8 Hz) p.p.m.; $[\alpha]_D$ ($CHCl_3$) +9°. Reduction of (**9**) and separation of the C-15 epimers on silica gel yielded (±)-(**9a**), m.p. 54—56°; (**9a**), m.p. 48—51°, $[\alpha]_D$ ($CHCl_3$) *ca.* 0°. (**9a**) on successive saponification and deacetalization afforded (±)-prostaglandin E_1 (**10**) (80—85%), m.p. 111—113°).[5] Similarly, natural series (**9a**) yielded (−)-prostaglandin E_1, m.p. 112—113°, $[\alpha]_D$ (THF) −59°§ identical with the natural product.

Repetition of this sequence in the enantiomeric series provided (+)-prostaglandin E_1, m.p. 112—113°, $[\alpha]_D$ (THF) +58°.§

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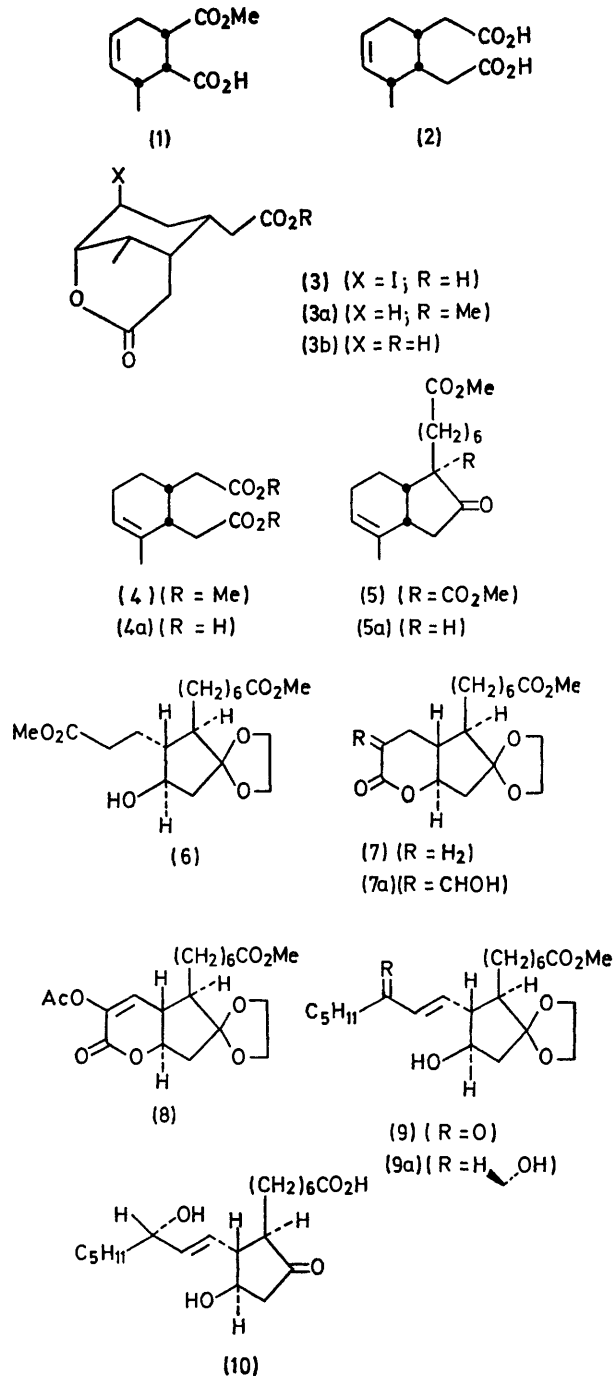

† Correct elemental analyses were obtained for all formulated compounds reported.

‡ The 2-monomethyl ester was prepared *via* an unrelated route by G. P. Kugatova-Shein-Yakina, V. M. Andrew, and S. A. Kazaryan *Zhur. org. Khim.*, 1966, **2**, 2025 (Engl. Trans.).

§ Natural (−)-prostaglandin E_1 and its (+)-enantiomer were prepared by total synthesis previously by E. J. Corey and collaborators; *cf.* E. J. Corey, I. Vlattas, and K. Harding, *J. Amer. Chem. Soc.*, 1969, **91**, 535; E. J. Corey, R. Noyori, and T. K. Schaaf, *ibid.*, 1970, **92**, 2586.

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