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AN EFFICIENT NEW APPROACH TO THE SYNTHESIS OF THE PROSTAGLANDINS. SYNTHESIS OF PGB_1

By C. H. Kuo, D. Taub and N. L. Wendler

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., Rahway, New Jersey 07065

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A synthetic route to the prostaglandins was sought which would be shorter and more efficient than those previously reported from these Laboratories.[1] In consequence thereof a stereoselective total synthesis of (±) prostaglandin E_1 was achieved in essentially twelve integral steps *via* the following novel route and in an overall yield of 12% or greater.[2]

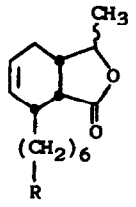
Diels-Alder condensation of methyl 8,10-undecadienoate[3] with β-angelica lactone (200°, 24 hrs) yielded **1** (75%) λ_{max}^{chf} 5.68, 5.78μ; nmr δ 1.37 (d, J=7 cps, H-C(CH$_3$)O-), 2.77 (m, 1H, H-C-CO$_2$-), 3.66 (s, 3H, -OCH$_3$), 4.20 (m, 1H, H-C(CH$_3$)-OCO), 5.6-6.0 (m, 2H, vinylic protons). Found: C, 69.67; H, 9.18%. Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90%. The structure of **1** was independently established by analogy with a model series in which the heptanoic acid side chain was replaced by methyl (to be published elsewhere). Oxidation of **1** (O_3-CH_2Cl_2, -65°/H_2O_2-HOAc, 55°) yielded the corresponding lactonic diacid (80%), mp 142-144°, Found: C, 57.02; H, 7.69%. Calcd. for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31%; the latter was in turn cyclized (Ac_2O, NaOAc)[4] with accompanying epimerization at C_2 to give the cyclopentanone lactone **2** (95%) λ_{max}^{chf} 5.66, 5.72, 5.78μ; nmr δ 1.43 (d, J=7 cps, H-C(CH$_3$)-O-), 3.66 (s, 3H, -OCH$_3$), 4.40 (m, 1H, H-C(CH$_3$)-OCO-).

Conversion of **2** (HO(CH$_2$)$_2$OH/PTSA) to its ketal derivative (Found: C, 63.39; H, 7.98%. Calcd. for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29%) followed by saponification (1N NaOH, CH_3OH/25°) afforded the corresponding lactonic acid (98%). In this con-

nection it was not found possible to open the lactone 1 in the presence of the CO_2R group thereby necessitating digression via the aldehyde acetal 3. Reduction of the acid as its acylimidazole derivative[5] with lithium tri-t-butoxyaluminium hydride followed by acetalization yielded the lactone bis-acetal 3 (89%) mp 43-46°; λ_{max}^{chf} 5.68, 10.55μ; nmr δ 1.33 (d, J=7 cps, H-C(CH$_3$)-O-), 3.92 (m, 8H, -O-CH$_2$CH$_2$-O-), 4.52 (m, 1H, H-C(CH$_3$)-O-), 4.87 (t, J=4 cps, 1H, -CH$_2$-HC-OCH$_2$CH$_2$-O-). Found: C, 63.78; H, 8.43%. Calcd. for $C_{19}H_{30}O_6$: C, 64.38; H, 8.53%. An alternative route to 3 involved the Diels-Alder product of β-angelica lactone with 1-acetoxy-8,10-undecadiene, the latter being derived from 8-acetoxysuberaldehyde and allyltriphenylphosphorane. Conversion of the product 1a to 2a was effected in a manner identical with the transformation 1→2. Hydrolysis of 2a (CH$_3$OH, HCl 25°) followed by oxidation (CrO_3-pyridine) and acetalization yielded 3.

Saponification of 3 (20% NaOH-CH$_3$OH/25°) followed by pH adjustment to 8-9 with CO_2 and ensuing oxidation (RuO_2-$NaIO_4$)[6] yielded the glycolic acid 4 quantitatively, nmr δ 3.93 (s, 4H, -OCH$_2$CH$_2$O-), 4.63 (s, 2H, -COOCH$_2$COOH), 7.93 (broad singlet, OH and COOH). Treatment of 4 with sodium methoxide in anhydrous methanol simultaneously effected the ester exchange and epimerization of the acetyl function to yield 5 (96%) λ_{max}^{chf} 2.8-3.3, 5.73, 5.80, 5.83, 10.52μ; nmr δ 2.20 (s, 3H, CH$_3$-C=O), 3.67 (s, 3H, -OCH$_3$), 3.93 (s, 4H, -OCH$_2$CH$_2$O-), 9.37 (broad singlet, 1H, CO_2H). Found: C, 60.39; H, 8.10%. Calcd. for $C_{18}H_{28}O_7$: C, 60.66; H, 7.92%.

Baeyer-Villiger oxidation (CF_3CO_3H, Na_2HPO_4) of 5 afforded 6 (95%), λ_{max}^{chf} 2.8-3.3, 5.75, 5.80, 5.83, 10.55μ; nmr δ 2.05 (s, 3H, CH$_3CO_2$-), 3.67 (s, 3H, -OCH$_3$), 3.97 (s, 4H, -OCH$_2$CH$_2$O-), 5.24 (m, 1H, H-C-OCOCH$_3$), 9.90 (broad singlet, 1H, COOH). Found: C, 57.73; H, 7.59%. Calcd. for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58%. The acid 6 was reduced via its acylimidazole derivative (LiAl(Ot-Bu)$_3$H) to the corresponding aldehyde (81%) and the latter directly converted via Wittig coupling ($C_5H_{11}COCH_2PO$-(OMe)$_2$, NaH, THF) to the 15-dehydro PGE_1 derivative 7 (71%). The overall yield of 7 was 25% or greater. This intermediate 7 was identical with material previously prepared by another route and converted in better than 50% yield to prostaglandin E_1.[1]



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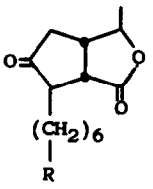
1a R = CH_2OAc



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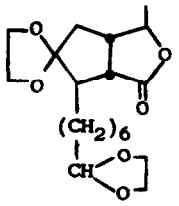
2a R = CH_2OAc



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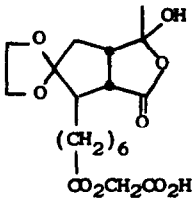

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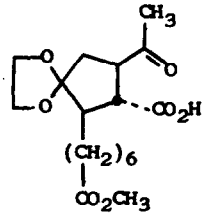

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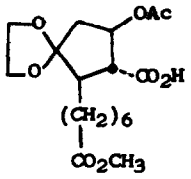

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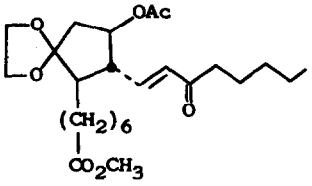

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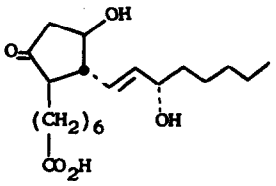

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