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THE SYNTHESIS OF dl-PROSTAGLANDIN E_1 METHOXIME

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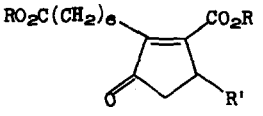
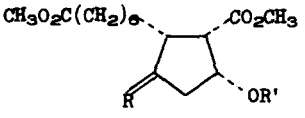
Several groups have recently reported on their prostaglandin synthesis (1), (2), (3), (4), and (5). We would now like to describe a new route to this interesting family of compounds. Out starting material is 2'-carboxy-5-oxo-cyclopent-1-eneheptanoic acid I,

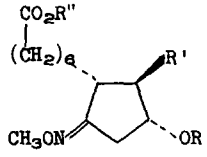


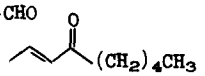
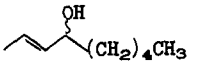
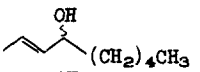
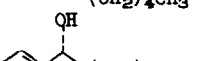


I	R = R' = H		VII	R = O,	R' = $Si(CH_3)_3$
II	R = CH_3,	R' = H	VIII	R = $NOCH_3$,	R' = H
III	R = CH_3,	R' = Br			
IV	R = CH_3,	R' = $OCOCH_3$			
V	R = CH_3,	R' = OH			
VI	R = CH_3,	R' = $OSi(CH_3)_3$			

[m.p. 95-6° (benzene)] which was prepared (6) (7) and allylically hydroxylated in a manner analogous to that for 2-methyl-3-oxo-1-cyclopentene carboxylic acid (8) (9). Reflux of the diester II [b.p. 146-9°|0.1 mm.; ν_{max}^{Film} 1735-1700(s) 1630(w) cm^{-1}; λ_{max}^{MeOH} 246 mμ (ϵ = 9,630); nmr ($CDCH_3$) 3.86 δ (s, 3) 3.66 δ (s, 3)] in carbon tetrachloride with N-bromosuccinimide and treatment of the crude bromo compound III with silver acetate in refluxing acetic acid gave IV [50% overall, b.p. 169-170°|0.01 mm.; ν_{max}^{Film} 1725(s) 1230(s)cm^{-1}, λ_{max}^{MeOH} 238 mμ (ϵ = 12,830) nmr ($CDCH_3$) 6.08 δ (m, 1) 3.88 δ (s, 3)]. Methanolysis of

of IV (2N MeOH|HCl) gave V [70%, b.p. 156-8°|0.01 mm.; ν_{max}^{Film} 3460(m) 1720(s) 1636(w) cm^{-1}, λ_{max}^{MeOH} 237 mμ (ϵ = 11,700); nmr ($CDCH_3$) 5.15 δ (m, 1) 3.92 δ (s, 3) 3.66 δ (s, 3)] which was further characterized as its semicarbazone (m.p. 140° aq. MeOH). Silylation and hydrogenation (Raney Ni|MeOH|40 lbs. in^{-2}) gave the crystalline siloxy cyclopentanone VII in almost quantitative yield. This is assigned the all cis configuration arising from cis addition of hydrogen from the side opposite to the bulky siloxy group. Reaction of VII with methoxyamine hydrochloride|pyridine gave a syn|anti mixture of methoximes (95%). The major isomer VIII was obtained by crystallization [70%, m.p. 46-7° (hexane), ν_{max}^{Nujol} 3380(m) 1730(s) 1655(w); nmr ($CDCH_3$) 4.48 δ (q, 1) 3.84 δ (s, 3) 3.72 δ (s, 3) 3.64 δ (s, 3)].



IX	R = H	R' = $-CO_2CH_3$	R" = CH_3
X	R = THP	R' = $-CO_2CH_3$	R" = CH_3
XI	R = THP	R' = $-CH_2OH$	R" = CH_2CH_3
XII	R = THP	R' = $-CHO$	R" = CH_2CH_3
XIII	R = THP	R' = 	R" = CH_2CH_3
XIV	R = THP	R' = 	R" = CH_2CH_3
XV	R = H	R' = 	R" = CH_2CH_3
XVI	R = H	R' = 	R" = H

Reflux of the methoxime VIII in methanolic K_2CO_3 gave a diacid which on reesterification gave a new methoxime diester IX (10) which is assigned an all trans configuration. (Epimerization α to the methoxime was regarded as unlikely based on model studies.) Reaction of IX with dihydropyran gave X (90%). Reduction of X by ethanolic $NaBH_4$ at R.T. selectively reduced the ester on the ring over the heptanoate ester. (11) The ester carbinol XI was purified by column chromatography on silica gel and obtained in 40% yield. Oxidation of XI to the aldehyde XII was accomplished almost quantitatively, by a modified Moffatt oxidation (12), using 1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide metho-p-toluenesulfonate (Aldrich C 10,640-2), as a catalyst and removing excess reagent by an ice water

wash. The aldehyde XII reacted in refluxing ether (under N_2) with 1-tributylphosphoranylidene-2-heptanone to give XIII (70%). Recent claims (2) notwithstanding this aldehyde and the derived hydroxyenone are very sensitive to elimination and use of the less reactive triphenyl phosphorane, necessitating more vigorous conditions, seemed inappropriate. Reduction of XIII with ethanolic sodium borohydride gave a mixture of allylic alcohols XIV. Removal of the tetrahydropyranyl group (aq. 1N HCl|MeOH R.T.) gave the diols XV, which were separated by preparative tlc (Alumina GF, eluted by cyclohexane|dioxan|ethyl acetate 7:2.5:0.5). The slower moving band was hydrolyzed by reflux in methanolic potassium carbonate, to give a crystalline acid XVI [m.p. 97-9° (aq. MeOH); $\nu_{max}^{MeCl_2}$ 3610(m) 3400(m) 1710(s) 1044(s) cm^{-1}; nmr ($CDCl_3$) 5.50 δ (m, 2) 4.05 δ (m, 1) 3.78 δ (s, 3); m.s. m|e (relative intensity) 383(2) 365(43) 347(57) 334(87) 147(100)]. PGE_1 (13) was converted to a syn|anti mixture of methoximes, which were separated on Mallinckrodt silicic acid (100-120 mesh, well washed [MeOH] and reactivated [120°|18 hrs]) using chloroform|methanol 99:1 as eluant. The faster moving isomer was crystallized (m.p. 55-7° [aq. MeOH]). The mass, IR and nmr spectra of this substance were indistinguishable from those of our synthetic compound XVI, as was its mobility on tlc (Silica eluted by $CHCl_3$|MeOH|AcOH|H_2O, 90:8:1:0.7) (14). Despite successful cleavages of a model 3-hydroxy-cyclopentanone methoxime to the cyclopentanone, difficulties were encountered with XVI. After solution in ethyl pyruvate|aq. 13% $HClO_4$ 4:1 for two days at 0-4°C, and careful work-up, only a small amount of material was isolated (silicic acid column chromatography and preparative tlc) corresponding to dl PGE_1 (mobility on tlc, UV behavior with base). This material was still contaminated with reagent derived artefacts and failed to crystallize. In view of the disappointing behavior of a methoxime as a ketone protecting group a new oxime reagent was developed which can be removed under conditions mild enough for PGE_1 to survive. Our full paper will describe the use of this new reagent in our scheme.

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7. We would like to acknowledge help from Dr. R. Stephani with this process.

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10. The identity of this diester and subsequent non-crystalline compounds was established by IR, nmr and where appropriate UV spectra. Their homogeneity was checked by tlc. Satisfactory elemental analyses were obtained for all compounds for which melting point and boiling point values are given. These values are uncorrected.

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13. We are indebted to Professor D. A. van Dorp (Unilever, Vlaardingen, Holland) for a very generous gift of PGE_1 and to Drs. Samuelsson and Pike for smaller reference samples.

14. We would like to acknowledge help from Swiss colleagues, during a stay by one of us (N.F.) in Basle. Dr. J. Schmidlin (CIBA) obtained excellent IR spectra with 1 mg., Dr. H. Hürzeler (CIBA) obtained mass spectra and Dr. U. Scheidegger (Varian) obtained nmr spectra on 2 mg. by use of a CAT.