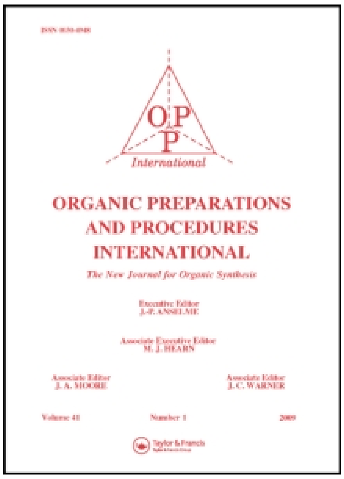

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SYNTHESIS OF METHYL 11,12-SECO-2,3-DINOR-10-OXAPROSTAGLANDIN E_1

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SYNTHESIS OF METHYL 11,12-SECO-2,3-DINOR-10-OXAPROSTAGLANDIN E_1

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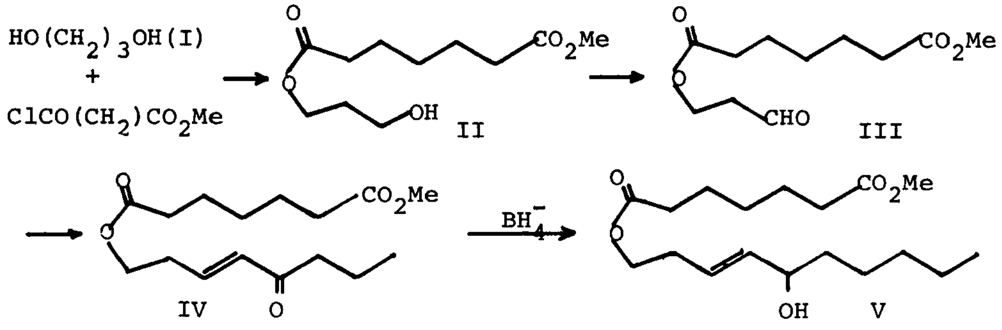
The synthesis of 10-oxaprostaglandin E_1 has been reported.[2] We would like to report herein the synthesis of methyl 11,12-seco-2,3-dinor-10-oxaprostaglandin E_1 as outlined below.



EXPERIMENTAL

Methyl 6-(3-hydroxy-1-propyloxycarbonyl)hexanoate (II).- To a solution of 1,3-propanediol I (20.4 g, 0.267 mol) and pyridine (10.6 g, 0.134 mol) in 300 ml of $CHCl_3$ cooled to 0° was added dropwise over a period of 1 hr. a solution of methyl 6-chloroformylhexanoate (12.9 g, 0.0669 mol) in 50 ml of chloroform; the reaction was stirred for an additional 24 hrs. at room temperature. The reaction mixture was extracted consecutively with two 100 ml portions of a 5% HCl solution, 150 ml of a 10% $NaHCO_3$ solution and 75 ml of water. The chloroform extract was dried ($MgSO_4$), filtered and concentrated on a rotatory evaporator to afford an oil. Distillation of the oil yielded 10.1 g (65%) of the ester-alcohol II, bp. 134-39° (0.1 mm): NMR (CCl_4) δ 4.16 (t, 2H), 3.64 (s) and 3.40-3.80 (m) [5H], 3.13 (s, broad, 1H), 2.08-2.50 (m, 4H) and 1.04-2.50 (m, 8H); ir (neat) 1735 (broad) cm^{-1}.

Anal. Calcd. for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.45; H, 8.55.

Methyl 6-(2-formyl-1-ethyloxycarbonyl)hexanoate (III).- The ester-alcohol II (5.0 g, 0.0216 mol) dissolved in a 1.5 liters of CH_2Cl_2 was placed in a three liter three-neck flask fitted with a mechanical stirrer and a nitrogen inlet tube and cooled to 0°. Collins reagent,[3] CrO_3•2 Py (31.6 g, 0.122 mol), was added all at once to the above solution and the reaction mixture was stirred at 0° for 1.5 hrs. under nitrogen. Powdered $NaHSO_4$•H_2O (67 g) was added all at once, and the stirring was continued at 0° for 25 mins. The reaction mixture was decanted into a separatory funnel and the reaction vessel was washed with additional CH_2Cl_2. The organic solutions were combined and washed consecutively with two 800 ml portions of a 10% HCl solution, 800 ml of a 10% $NaHCO_3$ solution and 100 ml of water. The methylene chloride solution was dried ($MgSO_4$), filtered, and concentrated on a rotatory evaporator to afford 4.6 g of crude ester-aldehyde III, NMR (CCl_4) δ 9.68 (t, J=2.3 Hz, 1H), 4.32 (t, 2H), 3.61 (s, 3H), 2.80 and 2.83 (triplets, 2H), 2.05-2.48 (m, 4H) and 1.05-1.95 (m, 6H); ir (neat) 1735 (broad), cm^{-1}. The aldehyde was not characterized further but subjected directly to the Wadsworth-Emmons reaction.

Methyl 8,12-seco-11-deoxy-2,3-dinor-15-oxo-10-oxa-PGE_1 (IV).- A three-neck flask fitted with an addition funnel, nitrogen inlet tube, magnetic stirring bar, and serum cap was flamed and deaerated with nitrogen. Dimethyl-(2-oxoheptyl)-phosphonate (2.9 g, 0.0130 mol) dissolved in 60 ml of dry THF was placed in the reaction vessel under nitrogen and cooled to 0°. A hexane solution of 2.29 M n-BuLi (6.27 ml, 0.01435 mol) was added with a syringe and the reaction was allowed to stir at 0° for 20 mins. The ester-aldehyde III (3.0 g, 0.01303 mol) dissolved in 30 ml of dry THF, was added to the reaction all at once at 0° and the resulting mixture was allowed to stir at

0° for 4.5 hrs. The solvent was removed on a rotatory evaporator and the residue was dissolved in 200 ml of CH_2Cl_2. The methylene chloride solution was extracted with 100 ml of water, dried ($MgSO_4$) filtered, and concentrated on a rotatory evaporatory to afford an oil. The oil was chromatographed on silica gel G and eluted with ether-hexane solutions to yield 2.9 g (67%) of the enone IV, NMR (CCl_4) δ 6.81 and 6.53 (triplets, 1H, J_{12-13}=6.8 Hz, J_{13-14}=16.5 Hz), 6.04 (d, 1H, J_{13-14}=16.5 Hz), 4.14 (t, 2H), 3.60 (s, 3H), 2.09-2.95 (m, 8H), 1.15-1.95 (m, 12H) and 0.89 (t, distorted, 3H); ir (neat) 1750, 1700, 1680 and 1640 cm^{-1}.

Anal. Calcd. for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 66.37; H, 9.17.

Methyl 8,12-seco-11-deoxy-2,3-dinor-10-oxa-PGE_1 (V).- A three-neck flask fitted with two addition funnels, a magnetic stirring bar and a nitrogen inlet tube was flamed and deaerated with nitrogen. $NaBH_4$ (0.280 g, 0.00736 mol) was placed in the reaction vessel and the vessel was cooled in CCl_4-Dry Ice. Dry methanol was added to obtain a clear methanolic-$NaBH_4$ solution. The enone IV (1.2 g, 0.00368 mol) dissolved in 30 ml of dry methanol was added dropwise over 10 min. and the resulting mixture was stirred for 3.5 hrs. at -23°. The reaction mixture was poured into an aqueous NaCl-Et_2O mixture (250 ml of ether and 250 ml of a saturated NaCl solution). The organic layer was separated and the aqueous solution was extracted with two 250 ml portions of ether. The ether extracts were combined and washed with 200 ml of H_2O. The ether solution was dried ($MgSO_4$), filtered, and concentrated on a rotatory evaporatory to afford an oil. The oil was chromatographed on silica gel G and eluted with ether-hexane solutions to yield 1.1 g (91%) of the ester-alcohol V,[4] NMR (CCl_4) δ 5.33-5.69 (m, 2H), 4.07 (t) and 3.75-4.25 (m) [3H], 3.63 (s, 3H), 2.84 (s, broad, 1H), 1.95-2.53 (m, 6H), 1.18-1.92 (m) and 0.92 (t) [17H]; ir (neat) 3500 (broad) and 1725 cm^{-1}.

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