

SYNTHESIS OF

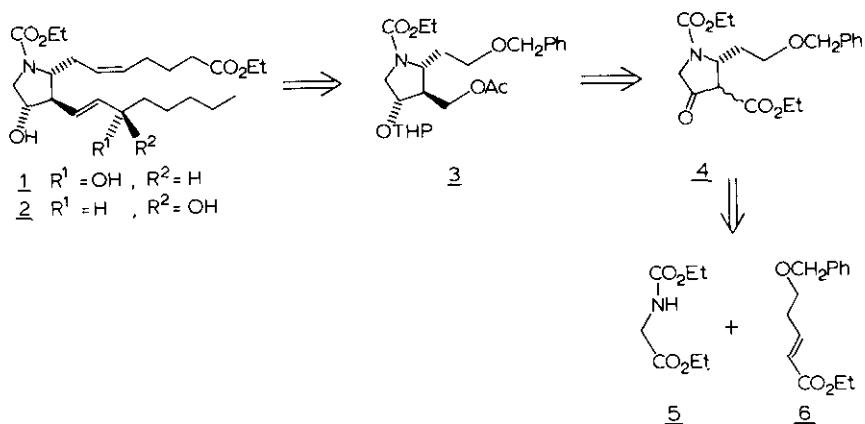
9-DEOXY-9-ETHOXYCARBONYL-9-AZAPROSTAGLANDIN E₂ ETHYL ESTERGerard P. Rozing, Johannes Kip, Willem Edam,Henk de Koning*, and Henderikus O. HuismanLaboratory of Organic Chemistry, University of Amsterdam,Nieuwe Achtergracht 129, Amsterdam, The Netherlands

9-Deoxy-9-ethoxycarbonyl-9-azaprostaglandin E₂ ethyl ester 1 and its C₁₅-epimer 2 were synthesized from the readily available protected triol 3 by selective deprotection of successive hydroxyl functions and subsequent side chain construction.

In view of their high but indiscriminate biological activity and their instability in vivo, the natural prostaglandins have called for synthesis of analogs. Since their structural elucidation (1) and first total syntheses (2) a great number of research workers have done so successfully (3). Our contribution in this field has led to the synthesis of 10,10-dimethyl-prostaglandins (4), 9 α -homoprostaglandins (5) and prostaglandin analogs in which the alicyclic five-membered ring is replaced by the pyrrolidine moiety (6a, 7a, 7b, 9). Analogs containing a nitrogen atom at ringposition 8 (6), 9 (7), 10 (8), 11 (9) and 12 (10) have been reported in the literature. In this communication we wish to describe the synthesis of 9-deoxy-9-azaprostaglandin E₂ analogs 1 and 2.

Application of the wellknown strategy in prostaglandin total synthesis viz. side chain construction by Wittig reaction of appropriate phosphoranes (phosphonates) with an aldehyde function (11), compelled us to manipulate the protected triol 3 in such a way, that the required aldehyde functions could be

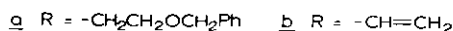
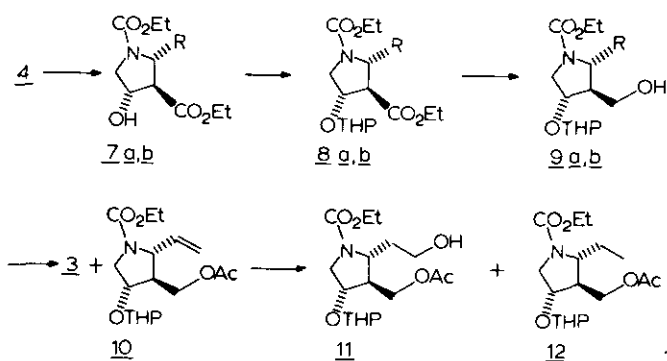
generated from the protected hydroxyl groups one by one. We expected the depicted protecting groups to meet this demand.



It was apparent from our previous work (7b) that 3 should easily be prepared from the β -oxo-ester 4, and our retrograde synthetic analysis was completed by ascertaining that 4 was to be synthesized from 5 and 6.

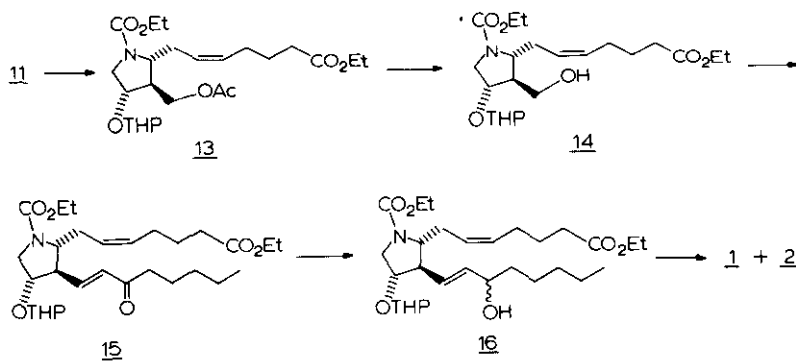
Michael-Dieckmann reaction [sodium hydride, benzene, 80°C, 2 h (7b, 12)] of ethyl N-ethoxycarbonylglycinate 5 with the substituted acrylic ester 6 (13) indeed afforded oxo-ester 4 [40%, IR (14) 1770, 1730, 1690, 1670, and 1640; ^1H NMR (14) 1.2 (m, $\text{COOCH}_2\text{CH}_3$), 3.5 (m, $\text{C}_{12}\text{-H}$ (15) of keto form, $\text{C}_6\text{-H}$), 4.75 (m, $\text{C}_8\text{-H}$ of enol form), and 7.2 (s, $\text{OCH}_2\text{C}_6\text{H}_5$)]. Stereoselective reduction of the carbonyl group (sodium cyanoborohydride, aqueous ethanol, pH 3) affording 7a [60%, IR 3450, 1720, and 1690; ^1H NMR 3.05 (t, $J_{8,12} = J_{11,12} = 5$, $\text{C}_{12}\text{-H}$), 3.32 (dd, $J_{10\alpha,11} = 5$, $J_{10\alpha,10\beta} = 11.5$, $\text{C}_{10}\text{-H}_\alpha$), 3.55 (m, $\text{C}_6\text{-H}$), 3.88 (dd, $J_{10\beta,11} = 6.5$, $J_{10\alpha,10\beta} = 11.5$, $\text{C}_{10}\text{-H}_\beta$), 4.47 (s, $\text{OCH}_2\text{C}_6\text{H}_5$), and 5.1 (m, $\text{C}_{11}\text{-H}$)] was complicated by unexpected formation of 7b [IR 3440, 1720, and 1680; ^1H NMR 1.24 and 1.28 (t, $J = 7$, $\text{COOCH}_2\text{CH}_3$), 2.86 (t, $J_{8,12} = J_{11,12} = 4.5$, $\text{C}_{12}\text{-H}$), 3.37 (dd, $J_{10\alpha,11} = 5.5$, $J_{10\alpha,10\beta} = 11.5$, $\text{C}_{10}\text{-H}_\alpha$), 4.55 (m, $\text{C}_8\text{-H}$), 5.05 - 5.35 (m, $\text{C}_6\text{-H}'\text{s}$), and 5.94 (m, $J_{6,7}(\text{trans}) = 16$, $J_{6,7}(\text{cis}) = 10$, $J_{7,8} = 6.5$, $\text{C}_7\text{-H}$); MS m/e (rel. abundance) 257 (52%), 184 (100%)] in varying amounts. Pure 7b could only be isolated by preparative gaschromatography (20% SE 30, chromosorb, 240°C). Facile elimination of

benzylalcohol from 7a is presumably brought about by anchimeric assistance of the amide function (16). Stereochemical assignments of the structures of 7a,b were based upon comparison of ^1H NMR data of 7a,b with ^1H NMR data of suitable model compounds (17). As column chromatographic separation of 7a and 7b was not possible but separation could be anticipated in a later stage of the synthesis after further transformations of 7a,b, the synthesis was continued with the mixture 7a,b. Tetrahydropyranylation (dihydropyran, p-toluenesulfonic acid in dichloromethane) furnishing 8a,b [100%; IR 1730, 1690, and 1120; ^1H NMR 8a 1.23 (t, $J = 7$, $\text{COOCH}_2\text{CH}_3$), 3.18 (m, $\text{C}_{12}\text{-H}$), 3.58 (m, $\text{C}_6\text{-H}$), 4.52 (s,



$\text{OCH}_2\text{C}_6\text{H}_5$), 4.7 (m, OCHO), and 5.1 (m, $\text{C}_{11}\text{-H}$); 8b 2.9 (m, $\text{C}_{12}\text{-H}$), 5.15 - 5.5 and 5.8 (m, $-\text{CH}=\text{CH}_2$)] was followed by reduction (sodium borohydride, ethanol, r.t., 16 h) of the C_{12} -ester function (18), thus producing the alcohols 9a,b [73%; IR 3450, 1690, and 1130; ^1H NMR 9a 1.24 (t, $J = 7$, $\text{NCOOCH}_2\text{CH}_3$), 2.35 (m, $\text{C}_{12}\text{-H}$), 3.28 (dd, $J_{10\alpha,11} = 4$, $J_{10\alpha,10\beta} = 12$, $\text{C}_{10}\text{-H}_\alpha$), 3.57 (m, $\text{C}_6\text{-H}$, $\text{C}_{13}\text{-H}$), 4.5 (s, $\text{OCH}_2\text{C}_6\text{H}_5$), 4.65 (m, OCHO), and 5.1 (m, $\text{C}_{11}\text{-H}$); 9b 5.2 - 5.5 and 5.8 (m, $\text{CH}=\text{CH}_2$)]. Subsequent acetylation (acetic anhydride, pyridine) of 9a,b afforded a mixture of the desired compound 3 with alkene 10 [85%; IR 1740, 1690, 1210, and 1130; ^1H NMR 3 1.20 (t, $J = 7$, $\text{NCOOCH}_2\text{CH}_3$), 2.0 (s, OCOCH_3), 2.5 (m, $\text{C}_{12}\text{-H}$), 3.55 (m, $\text{C}_6\text{-H}$), 4.05 (m, $\text{C}_{13}\text{-H}$), 4.5 (s, $\text{OCH}_2\text{C}_6\text{H}_5$), and 4.63 (m, OCHO); 10 5.2 - 5.5 and 5.8 (m, $\text{CH}=\text{CH}_2$)].

Hydrogenolysis of the benzyl ether was carried out under acidic conditions (ethyl acetate, acetic acid 10:1, Pd/C 10%, Parr apparatus) to give the alcohol 11 [83%, IR 3460, 1740, 1675, 1210, and 1130; ^1H NMR 1.20 (t, $J = 7$, $\text{NCOOCH}_2\text{CH}_3$), 2.0 (s, OCOCH_3), 3.55 (m, $\text{C}_6\text{-H}$), 4.05 (d, $J = 7$, $\text{C}_{13}\text{-H}$), 4.6 (m, OCHO); anal. $\text{C}_{17}\text{H}_{29}\text{NO}_7$ calc. 56.81% C, 8.13% H, 3.90% N, found 56.5% C, 8.1% H, 4.1% N], and 12 [60%; IR 1735, 1680, 1230, 1210, and 1120; ^1H NMR 0.9 (t, $J = 7$, $-\text{CH}_2\text{CH}_3$), 1.24 (t, $J = 7$, $\text{NCOOCH}_2\text{CH}_3$), 2.05 (s, OCOCH_3), 2.5 (m, $\text{C}_{12}\text{-H}$), 4.05 (d, $J = 7$, $\text{C}_{13}\text{-H}$), and 4.6 (m, OCHO)] which could easily be separated by column chromatography on silica gel.



Upper side chain construction was completed by Moffatt oxidation (19) [dimethylsulfoxide, 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate, trifluoroacetic acid, pyridine, and benzene] of 11, providing the corresponding aldehyde which, without further purification, was treated with the ylide prepared from triphenyl (4-carboxy-*n*-butyl)-phosphonium bromide (20) (dimethylsulfoxide, sodium hydride). Subsequent treatment of the crude product with diazoethane and purification through silica gel afforded the ester 13 [10% (21); IR 1735, 1690, 1220, and 1130; ^1H NMR 1.17, and 1.19 (t, $J = 7$, $\text{COOCH}_2\text{CH}_3$), 1.98 (s, OCOCH_3), 2.23 (t, $J = 7$, $\text{C}_2\text{-H}$), 2.45 (m, $\text{C}_{12}\text{-H}$), 3.95 (m, $\text{C}_{13}\text{-H}$), 4.55 (m, OCHO), and 5.25 - 5.55 (m,

C_5 -H, C_6 -H)]. Ethanolysis of the acetate function in 13 (ethanol, potassium carbonate) gave the alcohol 14 [IR 3460, 1720, 1680, and 1130; ^1H NMR 1.24 (t, $J = 7$, $\text{COOCH}_2\text{CH}_3$), 2.18 (t, $J = 7$, C_2 -H), 3.6 (m, C_{13} -H), 4.62 (m, OCHO), and 5.3 - 5.6 (m, C_5 -H, C_6 -H)] which was subjected to Moffatt oxidation (dimethylsulfoxide, 1-cyclohexyl-3-(2-morpholinoethyl)carbo-diimide metho-p-toluenesulfonate, trifluoroacetic acid, pyridine, and benzene), and subsequent Wittig-Horner reaction [dimethyl 2-oxoheptylphosphonate, sodium hydride, tetrahydrofuran (22)]. Upon column chromatography, enone 15 was isolated [64%; IR 1730, 1690, 1630, and 1130; ^1H NMR 0.89 (t, $J = 7$, C_{20} -H), 1.25 and 1.27 (t, $J = 7$, $\text{COOCH}_2\text{CH}_3$), 2.29 (t, $J = 7$, C_2 -H), 2.52 (t, $J = 8$, C_{16} -H), 2.75 (m, C_{12} -H), 3.30 (dd, $J_{10\alpha,11} = 5.5$, $J_{10\alpha,10\beta} = 11.0$, C_{10} -H $_{\alpha}$), 4.61 (m, OCHO), 5.3 - 5.6 (m, C_5 -H, C_6 -H), 6.16 (d, $J = 16$, C_{14} -H), and 6.68 (dd, $J = 16$, $J = 8$, C_{13} -H). Reduction of the C_{15} -carbonyl group [zinc borohydride, dimethoxyethane (23)] gave a mixture of C_{15} -epimeric alcohols 16 [73%, IR 3480, 1725, 1690, and 1130; ^1H NMR 0.87 (t, $J = 7$, C_{20} -H), 1.23 and 1.25 (t, $J = 7$, $\text{COOCH}_2\text{CH}_3$), 2.28 (t, $J = 7$, C_2 -H), 3.20 (m, C_{10} -H $_{\alpha}$), 4.63 (m, OCHO), 5.4 (m, C_5 -H, C_6 -H), 5.55 (m, C_{13} -H, C_{14} -H)] which was easily separated after hydrolysis of the tetrahydropyranyl ether (acetic acid/water/tetrahydrofuran 10:10:3, 50°C, 4 h), affording the prostaglandin analogs (+)-1 (24) [40%, IR 3420, 1720, 1675; ^1H NMR 0.88 (t, $J = 7$, C_{20} -H), 1.26 (t, $J = 7$, $\text{COOCH}_2\text{CH}_3$), 2.29 (t, $J = 7$, C_2 -H), 5.35 - 5.45 (m, C_5 -H, C_6 -H), 5.45 - 5.60 (m, C_{13} -H, C_{14} -H); anal. $C_{24}H_{41}NO_6$ calc. 65.57% C, 9.40% H, 3.10% N; found 65.2% C, 9.4% H, 3.0% N] and (+)-2 [30%, IR 3440, 1720, 1675; ^1H NMR 0.9 (t, $J = 7$, C_{20} -H), 1.26 (t, $J = 7$, $\text{COOCH}_2\text{CH}_3$), 2.31 (t, $J = 7$, C_2 -H), 5.35 - 5.50 (m, C_5 -H, C_6 -H), 5.55 - 5.65 (m, C_{13} -H, C_{14} -H); anal. found 65.5% C, 9.4% H, 3.3% N].

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