SYNTHESIS OF 9-DEOXY-9-ETHOXYCARBONYL-9-AZAPROSTAGLANDIN E_2 ETHYL ESTER

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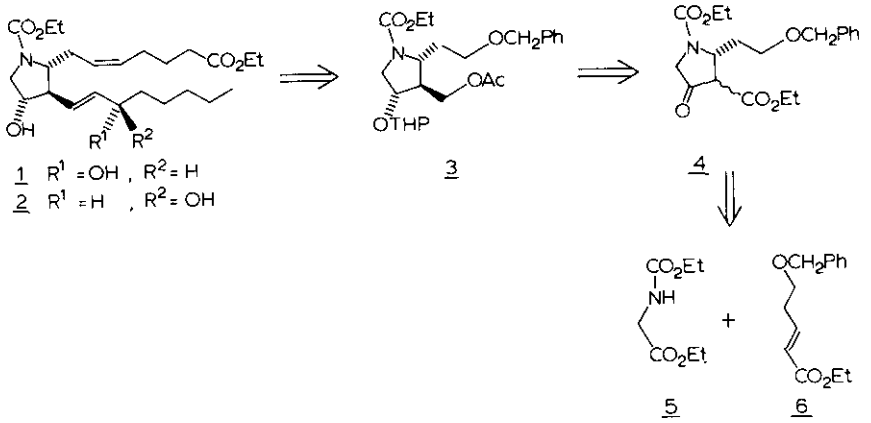
9-Deoxy-9-ethoxycarbonyl-9-azaprostaglandin E_2 ethyl ester 1 and its C_{15}-epimer 2 were synthesized from the readily available protected triol 3 by selective deprotection of successive hydroxyl functions and subsequent side chain construction.

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), 9a-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 E_2 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.



1 R^1 = OH, R^2 = H
2 R^1 = H, R^2 = OH

3

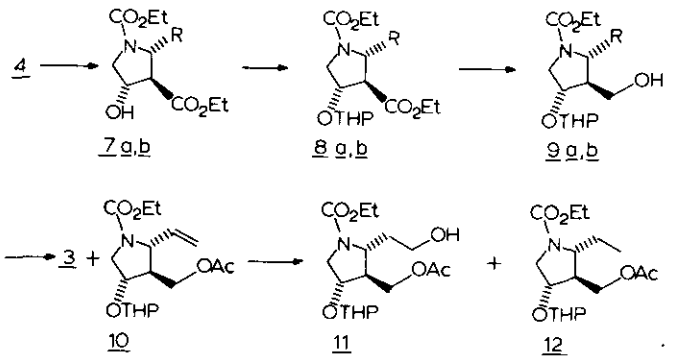
4

5 6

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; ^{1}H NMR (14) 1.2 (m, $COOCH_2\underline{CH}_3$), 3.5 (m, C_{12}-H (15) of keto form, C_6-H), 4.75 (m, C_8-H of enol form), and 7.2 (s, $OCH_2C_6\underline{H}_5$)]. Stereoselective reduction of the carbonyl group (sodium cyanoborohydride, aqueous ethanol, pH 3) affording 7a [60%, IR 3450, 1720, and 1690; ^{1}H NMR 3.05 (t, $J_{8,12} = J_{11,12} = 5$, C_{12}-H), 3.32 (dd, $J_{10\alpha,11} = 5$, $J_{10\alpha,10\beta} = 11.5$, C_{10}-H_α), 3.55 (m, C_6-H), 3.88 (dd, $J_{10\beta,11} = 6.5$, $J_{10\alpha,10\beta} = 11.5$, C_{10}-H_β), 4.47 (s, $OC\underline{H}_2C_6H_5$), and 5,1 (m, C_{11}-H)] was complicated by unexpected formation of 7b [IR 3440, 1720, and 1680; ^{1}H NMR 1.24 and 1.28 (t, J = 7, $COOCH_2\underline{CH}_3$), 2.86 (t, $J_{8,12} = J_{11,12} = 4.5$, C_{12}-H), 3.37 (dd, $J_{10\alpha,11} = 5.5$, $J_{10\alpha,10\beta} = 11.5$, C_{10}-H_α), 4.55 (m, C_8-H), 5.05 - 5.35 (m, C_6-H's), and 5.94 (m, $J_{6,7}$(trans) = 16, $J_{6,7}$(cis) = 10, $J_{7,8} = 6.5$, C_7-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

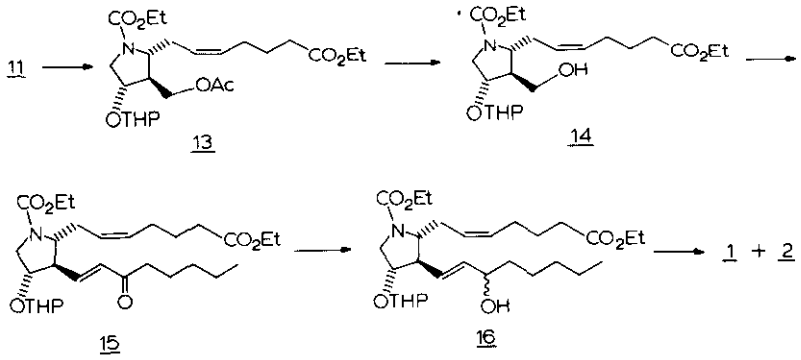
benzylalcohol from 7a is presumably brought about by anchimeric assistance of the amide function (16). Stereochemical assignments of the structures of 7a,b were based upon comparison of ^{1}H NMR data of 7a,b with ^{1}H NMR data of suitable model compounds (17). As column chromatographic separation of 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; ^{1}H NMR 8a 1.23 (t, J = 7, $COOCH_2\underline{CH}_3$), 3.18 (m, C_{12}-H), 3.58 (m, C_6-H), 4.52 (s,



a R = $-CH_2CH_2OCH_2Ph$ b R = $-CH=CH_2$

$OC\underline{H}_2C_6H_5$), 4.7 (m, OCHO), and 5.1 (m, C_{11}-H); 8b 2.9 (m, C_{12}-H), 5.15 - 5.5 and 5.8 (m, $-C\underline{H} = C\underline{H}_2$)] 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; ^{1}H NMR 9a 1.24 (t, J = 7, $NCOOCH_2\underline{CH}_3$), 2.35 (m, C_{12}-H), 3.28 (dd, $J_{10\alpha,11}$ = 4, $J_{10\alpha,10\beta}$ = 12, C_{10}-H_α), 3.57 (m, C_6-H, C_{13}-H), 4.5 (s, $OC\underline{H}_2C_6H_5$), 4.65 (m, OCHO), and 5.1 (m, C_{11}-H); 9b 5.2 - 5.5 and 5.8 (m, $C\underline{H} = C\underline{H}_2$)]. 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; ^{1}H NMR 3 1.20 (t, J = 7, $NCOOCH_2\underline{CH}_3$), 2.0 (s, $OCOCH_3$), 2.5 (m, C_{12}-H), 3.55 (m, C_6-H), 4.05 (m, C_{13}-H), 4.5 (s, $OC\underline{H}_2C_6H_5$), and 4.63 (m, OCHO); 10 5.2 - 5.5 and 5.8 (m, $C\underline{H} = C\underline{H}_2$)].

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; ^{1}H NMR 1.20 (t, J = 7, $NCOOCH_2\underline{CH_3}$), 2.0 (s, $OCOCH_3$), 3.55 (m, C_6-H), 4.05 (d, J = 7, C_{13}-H), 4.6 (m, OCHO); anal. $C_{17}H_{29}NO_7$ 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; ^{1}H NMR 0.9 (t, J = 7, $-CH_2\underline{CH_3}$), 1.24 (t, J = 7, $NCOOCH_2\underline{CH_3}$), 2.05 (s, $OCOCH_3$), 2.5 (m, C_{12}-H), 4.05 (d, J = 7, C_{13}-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; ^{1}H NMR 1.17, and 1.19 (t, J = 7, $COOCH_2\underline{CH_3}$), 1.98 (s, $OCOCH_3$), 2.23 (t, J = 7, C_2-H), 2.45 (m, C_{12}-H), 3.95 (m, C_{13}-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; ^{1}H NMR 1.24 (t, J = 7, $COOCH_2\underline{CH}_3$), 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)carbodiimide 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; ^{1}H NMR 0.89 (t, J = 7, C_{20}-H), 1.25 and 1.27 (t, J = 7, $COOCH_2\underline{CH}_3$), 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_α), 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; ^{1}H NMR 0.87 (t, J = 7, C_{20}-H), 1.23 and 1.25 (t, J = 7, $COOCH_2\underline{CH}_3$), 2.28 (t, J = 7, C_2-H), 3.20 (m, C_{10}-H_α), 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; ^{1}H NMR 0.88 (t, J = 7, C_{20}-H), 1.26 (t, J = 7, $COOCH_2\underline{CH}_3$), 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; ^{1}H NMR 0.9 (t, J = 7, C_{20}-H, 1.26 (t, J = 7, $COOCH_2\underline{CH}_3$), 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].

ACKNOWLEDGEMENT: We thank the Ministry of Social Affairs for financial support to one of us (W.E.).

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Received, 19th October, 1978