SYNTHESIS OF 11-AZAPROSTAGLANDIN ANALOGS

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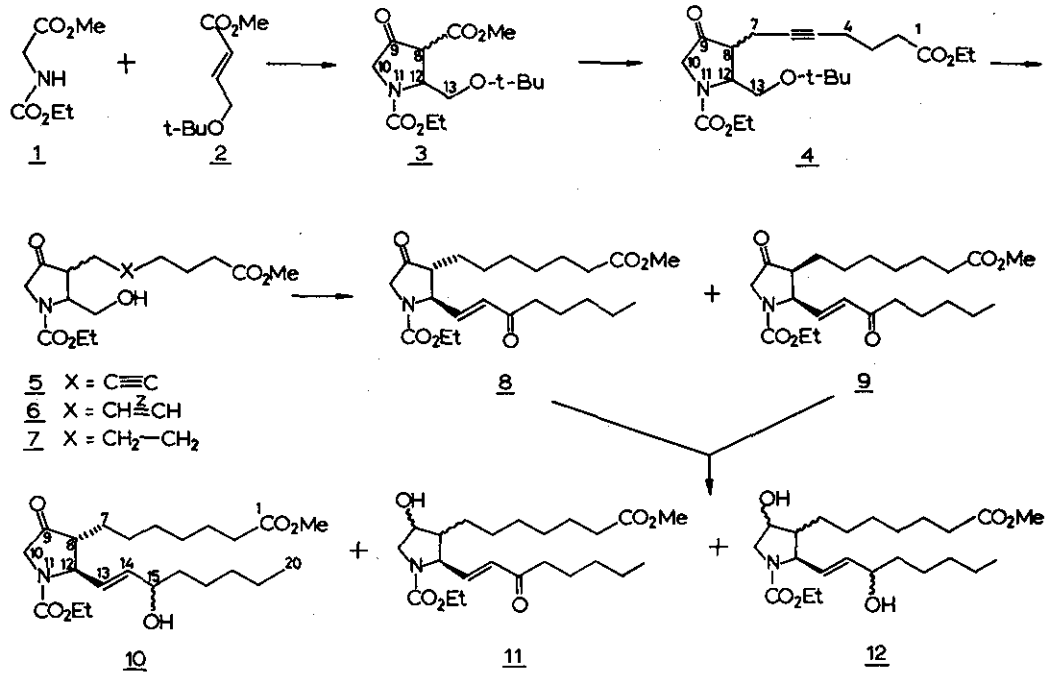
11-Deoxy-11-azaprostaglandin derivatives are obtained in eight steps, starting from methyl N-ethoxycarbonylglycinate and ethyl 4-tert-butoxycrotonate. The synthesis of an aza-analog of the "Corey-lactone" is described.

Recently several reports have appeared in the literature on the synthesis of prostaglandin analogs containing a nitrogen atom or atoms in ring positions 8 (2), 9 (3), 10 (4), 12 (5), or 8,12 (6). So far 11-azaprostaglandin analogs have not been described, and in this communication we wish to report our results in this field.

Ethoxycarbonylpyrrolidone 3 [IR ($CHCl_3$) 1760, 1720, 1690, 1670, 1630, and 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (s, $C(CH_3)_3$), 3.35 (d, $J_{8,12}$= 2Hz, C_8-H of keto form (7)), 3.4 and 3.85 (m, C_{13}-H), and 4.7 (m, C_{12}-H of enol form)] was obtained in 46% yield by Michael reaction and subsequent Dieckmann cyclization (8) of methyl N-ethoxycarbonylglycinate 1 and methyl 4-tert-butoxycrotonate 2 (9) with sodium hydride in benzene at 80° for 2 h. The potassium salt of β-keto-ester 3, prepared from 3 and potassium hydroxide in



ethanol, was dissolved in dimethyl sulfoxide and alkylated with ethyl 7-bromo-5-heptynoate (10) at ambient temperature. Demethoxycarbonylation with lithium iodide in hexamethylphosphoric triamide at 120° afforded pyrrolidone 4 [46%; IR ($CHCl_3$) 1765, 1730, 1690, and 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (s, $C(CH_3)_3$), 1.75 (m, C_3-H), 2.1-2.4 (m, C_2-H, C_4-H), 2.45 (m, C_7-H), 2.6 (m, C_8-H), and 3.8 (m, C_{10}-H)] as an inseparable mixture of cis, trans isomers.

Cleavage of the tert-butyl ether in 4 with boron trifluoride etherate in acetic anhydride, followed by methanolysis in the presence of potassium carbonate and purification through a silica gel column, provided alcohol 5 [72%; IR ($CHCl_3$) 3450, 1765, 1730, and 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (m, C_3-H), 2.10-2.45 (m, C_2-H, C_4-H), 2.55 (m, C_7-H), 3.68 (s, CO_2CH_3), and 3.9 (m, C_{13}-H)]. Partial hydrogenation of 5 over 5% palladium on barium sulfate in methanol at atmospheric pressure furnished Z-olefin 6 [85%; IR

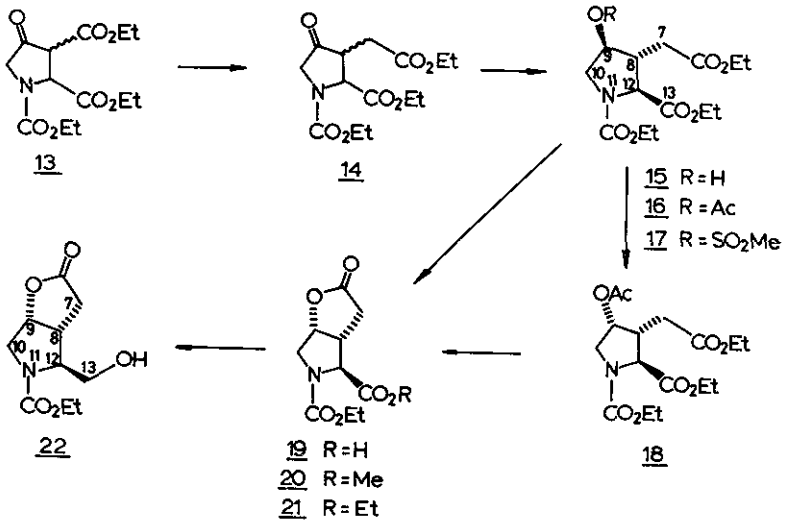
($CHCl_3$) 3450, 1765, 1730, and 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65 (m, C_3-H), 3.65 (s, CO_2CH_3), 3.85 (m, C_{13}-H), and 5.42 (m, C_5-H, C_6-H)], while the saturated compound 7 [70%; IR ($CHCl_3$) 3450, 1765, 1730, and 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (t, J= 7 Hz, C_2-H), 2.45 (m, C_8-H), 3.68 (s, CO_2CH_3), and 3.87 (m, C_{13}-H)] was obtained upon hydrogenation over palladium on charcoal in methanol at 3-4 atm. Both compounds, 6 and 7, were obtained as an inseparable mixture of cis and trans isomers.

Moffatt oxidation [dimethyl sulfoxide, 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate, trifluoroacetic acid, pyridine, and benzene] of alcohol 7 and subsequent reaction of the aldehyde, thus obtained, with the anion of dimethyl 2-oxoheptylphosphonate in tetrahydrofuran gave in 71% yield a mixture of enones 8 [IR ($CHCl_3$) 1760, 1730, 1700, 1680, and 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, J= 7 Hz, C_{20}-H), 2.25 (t, J= 7 Hz, C_2-H), 2.50 (t, J= 7 Hz, C_{16}-H), 3.63 (s, CO_2CH_3), 4.6 (m, C_{12}-H), 6.15 (d, $J_{13,14}$= 16 Hz, C_{14}-H), and 6.60 (dd, $J_{13,14}$= 16 Hz, $J_{12,13}$= 8 Hz, C_{13}-H)] and 9 [^1H NMR ($CDCl_3$) δ 5.0 (m, C_{12}-H), 6.19 (d, $J_{13,14}$= 16 Hz, C_{14}-H), and 6.60 (dd, $J_{13,14}$= 16 Hz, $J_{12,13}$= 8 Hz, C_{13}-H)]. Configurational assignment of 8 and 9 was based upon the chemical shifts of the C_{12}-H's and the vicinal coupling constants $J_{8,12}$ (11), which were 4 Hz (8) and 7 Hz (9), in agreement with the corresponding spectral data of model compounds (12).

In order to achieve selective reduction of the C_{15} carbonyl function (13) the mixture of enones was treated with lithium tri-sec-butylborohydride in tetrahydrofuran at -78°. However, upon column chromatography on silica gel, besides some starting material, a fraction containing hydroxyketones 10 and 11, and a fraction containing 11-aza-PGF_1 isomers 12 [45%; IR ($CHCl_3$) 3450, 1730, and

1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, J= 7 Hz, C_{20}-H), 2.32 (t, J= 7 Hz, C_2-H), 3.7 (s, CO_2CH_3), and 5.62 (m, C_{13}-H , C_{14}-H)] were isolated. Preparative layer chromatography of the hydroxyketone fraction gave a C_{15} epimeric mixture of 11-aza-PGE_1 analog 10 [18%; IR ($CHCl_3$) 3460, 1760, 1730, and 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, J= 7 Hz, C_{20}-H), 2.32 (t, J= 7 Hz, C_2-H), 3.7 (s, CO_2CH_3), 4.5 (m, $\Delta\nu_{\frac{1}{2}}$= 7 Hz, C_{12}-H), and 5.65 (m, C_{13}-H, C_{14}-H)], while enone 11 decomposed.

Because the above synthesis lacks stereoselectivity a new reaction scheme was designed, leading to an aza-analog of the well-known "Corey-lactone"(14). The synthesis starts from the keto-ester 13 (8), obtained in 53% yield from ethyl N-ethoxycarbonylglycinate and diethyl fumarate according to the procedure described for 3. Alkylation of the potassium salt of 13 with ethyl bromoacetate in dimethyl sulfoxide at ambient temperature, followed by decarboxylation with aqueous hydrochloric acid in acetic acid at 110° and re-esterification with ethanol in the presence of sulfuric acid, provided a mixture of pyrrolidones 14 [IR ($CHCl_3$) 1760, 1740, and 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.7-3.0 (m, C_7-H, C_8-H)] in 40% yield after column chromatography on silica gel. Catalytic hydrogenation of 14 over platinum oxide in ethanol at 3-4 atm and subsequent chromatographic purification furnished the pure all-trans-hydroxy ester 15 [64%; IR ($CHCl_3$) 3500, 1720, and 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.56 (m, C_7-H, C_8-H), 3.45 (dd, $J_{9,10\beta}$= 4 Hz, $J_{10\alpha,10\beta}$= 11.5 Hz, $C_{10\beta}$-H), and 3.75 (br, exchangeable with D_2O, OH)]. The relative configuration was assigned after comparing ^1H NMR spectra of 15 and its acetate 16 with those of model compounds (12).



Hydroxy-ester 15 was converted with methanesulfonyl chloride in pyridine into the corresponding mesylate 17 [58%; IR ($CHCl_3$) 1730, 1690, 1340, and 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.55 (m, C_8-H), 3.05 (m, C_7-H; s, CH_3SO_2), 3.7 (dd, $J_{9,10\beta}$= 4 Hz, $J_{10\alpha,10\beta}$= 13 Hz, $C_{10\beta}$-H), and 5.05 (dt, $J_{8,9}$= $J_{9,10\beta}$= 4 Hz, $J_{9,10\alpha}$= 6 Hz, C_9-H)], which could be transformed in high yield into the lactone acid 19 [98%; IR ($CHCl_3$) 3400-2700, 1780, 1720, and 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.10 (m, C_9-H), and 6.0 (br, exchangeable with D_2O, CO_2H)] upon reaction with aqueous potassium hydroxide in tetrahydrofuran and subsequent acidification and heating at 60-80° for 3 h. In order to obtain better analyzable ^1H NMR spectra, lactone acid 19 was treated with diazomethane to afford lactone methyl ester 20 [IR ($CHCl_3$) 1780, 1740, and 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52-3.10 (m, C_7-H), 3.2 (m, C_8-H), 3.65 (m, $C_{10\alpha}$-H), 3.78 (s, CO_2CH_3), and 5.58 (m, C_9-H)].

Reaction of mesylate 17 with tetraethylammonium acetate in refluxing acetone produced inverted acetate 18 [67%; IR ($CHCl_3$) 1740, 1690, and 1220 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (s, CH_3CO), 3.65-3.8 (m, C_{10}-H), and 5.35 (m, C_9-H)] that could be converted into lactone ethyl ester 21 (85%) upon treatment with potassium hydroxide in aqueous ethanol and subsequent acidification and heating at ca. 70°.

Reduction of the carboxyl function in 19 with diborane in tetrahydrofuran afforded the "Corey-type" lactone alcohol 22 [50%; IR ($CHCl_3$) 3430, 1785, and 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, J= 7 Hz, $NCO_2CH_2\underline{CH_3}$), 2.45-3.05 (m, C_7-H), 3.08 (m, C_8-H), 3.7 (br, exchangeable with D_2O, OH), 3.7 (m, C_{13}-H), 4.14 (q, J= 7 Hz, $NCO_2\underline{CH_2}CH_3$), and 5.55 (m, C_9-H)] from which 11-azaprostaglandin analogs should be obtained by standard procedures (15).

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15 Conversion of lactone alcohol 22 into 11-azaprostaglandins is currently under investigation.

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