SYNTHESIS OF 9-AZAPROSTAGLANDIN ANALOGS

Gerard P. Rozing (1), Henk de Koning*, and Henderikus O. Huisman
Laboratory for Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands

9-Deoxy-9-azaprostaglandin analogs are obtained in eight steps, starting from ethyl N-ethoxycarbonylglycinate and diethyl 2-decenedioate.

We recently described the synthesis of 9,11-dideoxy-9-azaprostaglandins (2). In this communication we want to report the synthesis of 9-deoxy-9-azaprostaglandin analogs.

Key compound in the synthetic scheme is the pyrrolidone 3 [IR ($CHCl_3$) 1760, 1720, 1690, 1670, and 1630 cm^{-1}; NMR ($CDCl_3$) δ 2.30 (t, J = 7 Hz, $-CH_2COOEt$), 3.28 (d, $J_{8,12}$ = 3 Hz, C_{12}-H (3), keto form), 4.9 (m, C_8-H, enol form), 9.8 (br, OH, enol form)], obtained in 40% yield by Michael-Dieckmann reaction (4) (sodium hydride, benzene, 80°C, 2 hr) of ethyl N-ethoxycarbonylglycinate 1 and the substituted acrylic ester 2 (5). The enol form of 3 appeared to be the predominant tautomer as was deduced from the ^{1}H-NMR spectrum.

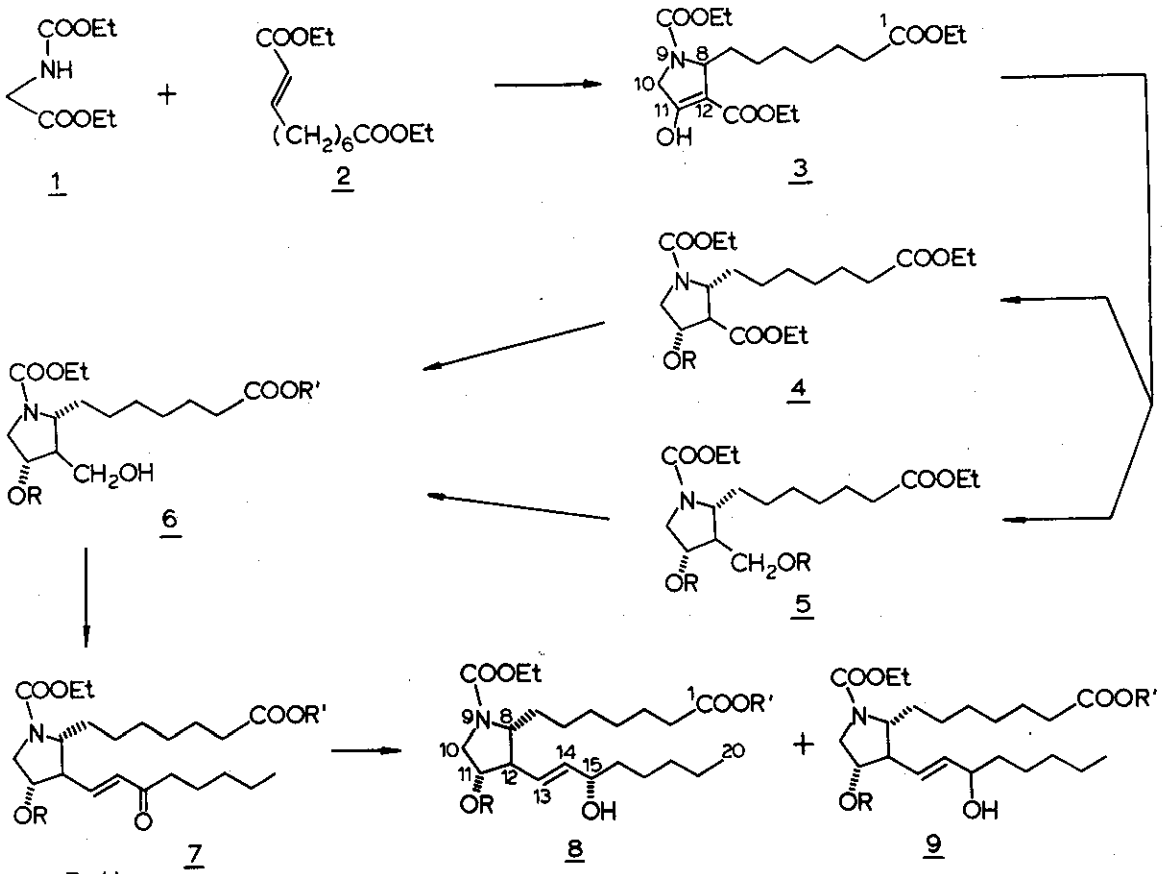
Conversion of the β-keto ester moiety into the mono-protected diol system with the appropriate relative configuration produced

the major problem in the synthetic scheme. Several reductions were performed with model compound 1,4-diethoxycarbonyl-5-methylpyrrolidin-3-one to find suitable reaction conditions (6). Both catalytic hydrogenation of 3 in ethanol over Adams catalyst and reduction with sodium cyanoborohydride at pH 3 (7) afforded in high yield a mixture of hydroxy esters, from which the predominant isomer 4a [IR ($CHCl_3$) 3500, 1730, and 1690 cm^{-1}; NMR ($CDCl_3$) δ 2.28 (t, J = 7 Hz, $-C\underline{H}_2COOEt$), 2.78 (t, $J_{8,12} = J_{11,12}$ = 5 Hz, C_{12}-H), 3.22 (d d, $J_{10\alpha,11}$ = 6 Hz, $J_{10\alpha,10\beta}$ = 11,5 Hz, C_{10}-H_α), 4.48 (m, C_{11}-H)] was isolated in pure form by column chromatography.

Reduction of 3 with sodium borohydride (0.6 mol equivalent) at -18°C gave a mixture of hydroxy esters, diols, and starting material. Reduction of 3 with a large excess of sodium borohydride (5 mol equivalent) at -18°C produced all-trans-diol 5a [55%; IR ($CHCl_3$) 3500, 1720, and 1690 cm^{-1}; NMR ($CDCl_3$) δ 2.1 (m, C_{12}-H), 2.28 (t, J = 7 Hz, $-C\underline{H}_2COOEt$), 3.18 (d d, $J_{10\alpha,11}$ = 6 Hz, $J_{10\alpha,10\beta}$ = 11,5 Hz, C_{10}-H_α), 3.45 (br, exchangeable with D_2O)] which was purified by column chromatography.

The C_{11}-hydroxy group of 4a could be protected as tetrahydropyranyl ether (dihydropyran, p-toluenesulfonic acid) 4b [95%, IR ($CHCl_3$) 1720, 1690, and 1020 cm^{-1}] or as tert-butyl ether (BF_3/H_3PO_4, isobutene) 4c [90%, IR ($CHCl_3$) 1720, 1690, and 1370 cm^{-1}].

Regioselective reduction of the C_{12}-ester moiety of 4b was achieved with an excess of sodium borohydride in ethanol at room



a R = H
b R = THP
c R = t-Bu
d R = Ac

temperature (8), providing 6b (R' = Et) [IR ($CHCl_3$) 3500, 1720, 1680, and 1020 cm^{-1}; NMR ($CDCl_3$) δ 2.15 (m, C_{12}-H), 2.28 (t, J = 7 Hz, -$C\underline{H}_2$COOEt), 3.15 (br, exchangeable with D_2O,-$CH_2O\underline{H}$), 3.58 (d, J = 6 Hz, -$C\underline{H}_2$OH)] in 45% yield after chromatography over silica gel.

Diol 5a could also be converted into a C_{11}-protected primary alcohol, 6d (R' = Me), in the following way. Reaction with acetic anhydride in pyridine afforded diacetate 5d [100%; IR ($CHCl_3$) 1730, 1690, and 1240 cm^{-1}; NMR ($CDCl_3$) δ 2.05 (s, OCOC$\underline{H}_3$), 4.12 (d, J = 7 Hz, -$C\underline{H}_2$OAc), 5.06 (d t, $J_{10\alpha,11}$ = 3 Hz, $J_{10\beta,11}$ = $J_{11,12}$ = 6 Hz, C_{11}-H)]. Acid catalysed methanolysis of 5d gave a mixture of 5a, 5d, and 6d in a ratio 20 : 50 : 30, which could easily be separated by column chromatography. After recycling of 5a and 5d, 6d (R' = Me) [IR ($CHCl_3$) 3500, 1730, 1690, and 1240 cm^{-1}; NMR ($CDCl_3$) δ 3.54 (d, J = 7 Hz, -$C\underline{H}_2$OH), 3.64 (s, -COOC$\underline{H}_3$), 5.11 (d t, $J_{10\alpha,11}$ = 3 Hz, $J_{10\beta,11}$ = $J_{11,12}$ = 6 Hz, C_{11}-H)] was obtained in 50% yield.

Moffatt oxidation [dimethyl sulfoxide, 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-p-toluenesulfonate, trifluoroacetic acid, pyridine and benzene (8)] of the C_{13}-alcohol function in 6b (R' = Et) yielded the corresponding aldehyde which - without further purification - was converted [dimethyl 2-oxoheptylphosphonate, sodium hydride, tetrahydrofuran (9)] into the enone 7b (R' = Et) [50%; IR ($CHCl_3$) 1720, 1680, 1620, and 1020 cm^{-1}; NMR ($CDCl_3$) δ 0.90 (t, J = 7 Hz, C_{20}-H_3), 2.28 (t, J = 7 Hz, -$C\underline{H}_2$COOEt), 2.54 (t, J = 7 Hz, -CO-$C\underline{H}_2$-), 2.8 (m, C_{12}-H), 6.20 (d, $J_{13,14}$ = 16 Hz, C_{14}-H), 6.70 (d d, $J_{12,13}$ = 8 Hz, $J_{13,14}$ = 16 Hz, C_{13}-H)].

Reduction of the C_{15}-carbonyl function in 7b (zinc borohydride, dimethoxyethane, room temperature) gave a mixture of the C_{15} epimeric alcohols 8b and 9b (R' = Et) [70%; IR ($CHCl_3$) 3450, 1720, 1680, and 1020 cm^{-1}; NMR ($CDCl_3$) δ 5.57 (m, C_{13}-H, C_{14}-H)] which were not separated. Hydrolysis of the tetrahydropyranyl ether was accomplished with acetic acid, water and tetrahydrofuran (10). The mixture of isomers, thus obtained in 70% yield, could be separated by column chromatography to give prostaglandin analog 8a (R' = Et) [IR ($CHCl_3$) 3450, 1720, and 1670 cm^{-1}; NMR ($CDCl_3$) δ 0.89 (t, J = 7 Hz, C_{20}-H_3), 2.28 (t, J = 7 Hz, -CH_2COOEt), 2.45 (m, C_{12}-H), 5.54 (m, C_{13}-H, C_{14}-H)] and its C_{15}-epimer 9a (R' = Et) (spectra very similar to 8a).

Tert-butyl ether 4c was converted by the same series of reactions into the mixture of allylic alcohols 8c and 9c (R' = Et). Cleavage of the tert-butyl ether with trifluoroacetic acid (11), followed by subsequent methanolysis of the trifluoroacetates gave the prostaglandin analogs. The C_{11}-acetoxy carbinol 6d (R' = Me) could also be converted into the allylic alcohols 8d and 9d (R' = Me) (12), which were deprotected by methanolysis in the presence of potassium carbonate to give 8a and 9a (R' = Me).

REFERENCES

1 Part of the forthcoming thesis of G.P. Rozing.

2 G.P. Rozing, T.J.H. Moinat, H. de Koning, and H.O. Huisman, Heterocycles, 1976, 4, 719.

3 Prostaglandin numbering throughout this communication.

4 R. Kuhn and G. Osswald, Chem. Ber., 1956, 89, 1423.

5 Prepared by a modified Rosenmund reduction of ethyl 7-chloroformylheptanoate followed by subsequent Wittig-Horner reaction of the aldehyde with triethyl phosphonoacetate.

6 Details will be reported in the full publication.

7 R.F. Borch, M.D. Bernstein, and H. Dupont Durst, J. Amer. Chem. Soc., 1971, 93, 2897.

8 N. Finch, L. DellaVecchia, J.J. Fitt, R. Staphani, and I. Vlattas, J. Org. Chem., 1973, 38, 4412.

9 E.J. Corey, N.M. Weinshenker, T.K. Schaaf, and W. Huber, J. Amer. Chem. Soc., 1969, 91, 5675.

10 E.L. Cooper and E.W. Yankee, ibid., 1974, 96, 5876.

11 E. Hardegger, H.P. Schenck, and E. Broger, Helv. Chim. Acta, 1967, 50, 2501.

12 Some elimination occurred in the Horner reaction.

Received, 7th August, 1976