

SYNTHESIS OF 9-AZAPROSTAGLANDIN ANALOGS

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9-Deoxy-9-azaprostaglandin analogs are obtained
in eight steps, starting from ethyl N-ethoxy-
carbonylglycinate 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 (CHCl₃) 1760, 1720, 1690, 1670, and 1630 cm⁻¹; NMR (CDCl₃) δ 2.30 (t, J = 7 Hz, -CH₂COOEt), 3.28 (d, J_{8,12} = 3 Hz, C₁₂-H (3), keto form), 4.9 (m, C₈-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 ¹H-NMR spectrum.

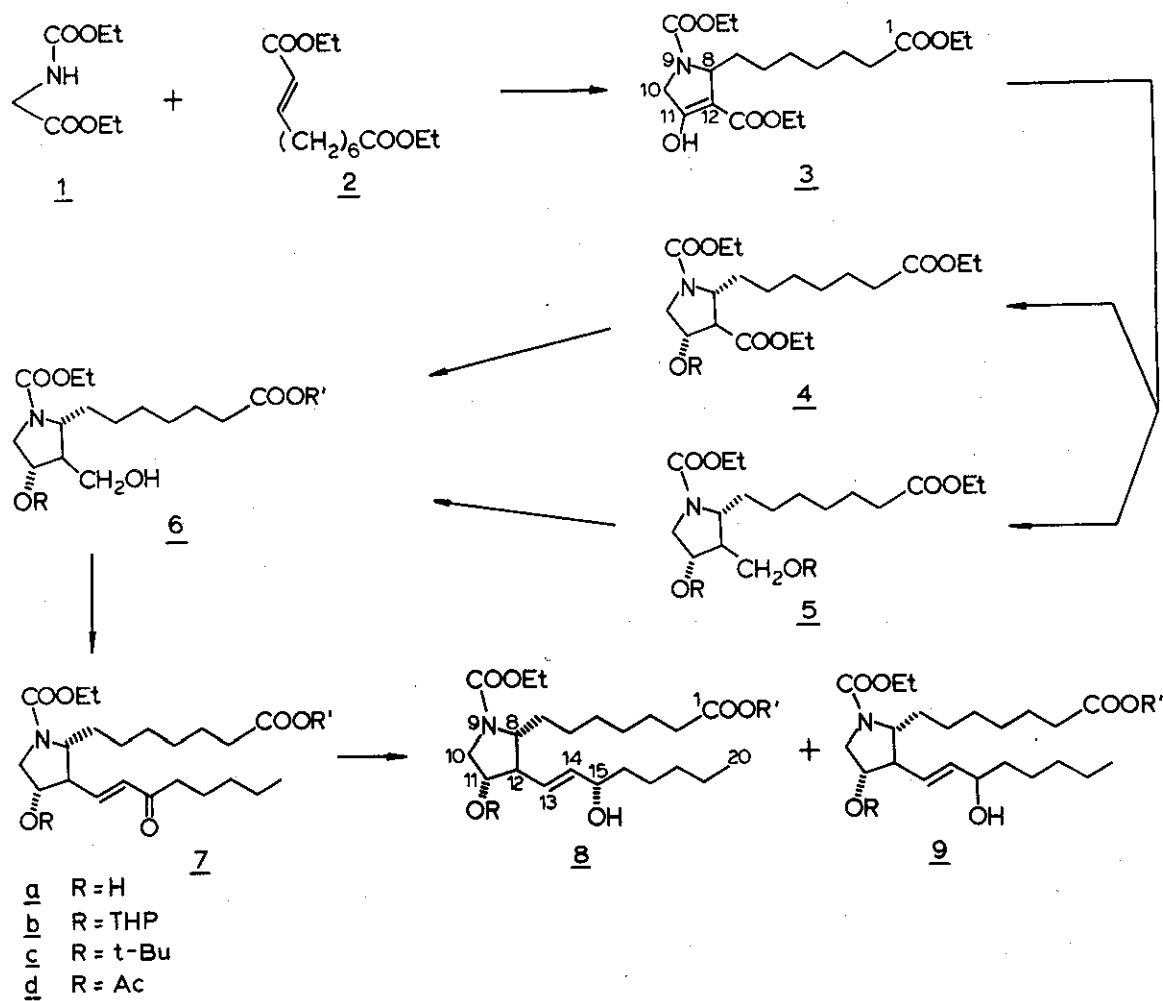
Conversion of the β-keto ester moiety into the mono-protected diol system with the appropriate relative configuration produced

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 (CHCl₃) 3500, 1730, and 1690 cm⁻¹; NMR (CDCl₃) δ 2.28 (t, J = 7 Hz, -CH₂COOEt), 2.78 (t, J_{8,12} = J_{11,12} = 5 Hz, C₁₂-H), 3.22 (d d, J_{10α,11} = 6 Hz, J_{10α,10β} = 11,5 Hz, C₁₀-H_α), 4.48 (m, C₁₁-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 (CHCl₃) 3500, 1720, and 1690 cm⁻¹; NMR (CDCl₃) δ 2.1 (m, C₁₂-H), 2.28 (t, J = 7 Hz, -CH₂COOEt), 3.18 (d d, J_{10α,11} = 6 Hz, J_{10α,10β} = 11,5 Hz, C₁₀-H_α), 3.45 (br, exchangeable with D₂O)] which was purified by column chromatography.

The C₁₁-hydroxy group of 4a could be protected as tetrahydropyranyl ether (dihydropyran, p-toluenesulfonic acid) 4b [95%, IR (CHCl₃) 1720, 1690, and 1020 cm⁻¹] or as tert-butyl ether (BF₃/H₃PO₄, isobutene) 4c [90%, IR (CHCl₃) 1720, 1690, and 1370 cm⁻¹].

Regioselective reduction of the C₁₂-ester moiety of 4b was achieved with an excess of sodium borohydride in ethanol at room



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

Diol 5a could also be converted into a C_{11} -protected primary alcohol, 6d ($R' = \text{Me}$), 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, OCOCH_3), 4.12 (d, $J = 7\text{ Hz}$, $-\text{CH}_2\text{OAc}$), 5.06 (d t, $J_{10\alpha,11} = 3\text{ Hz}$, $J_{10\beta,11} = J_{11,12} = 6\text{ Hz}$, $\text{C}_{11}\text{-H}$)]. 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 ($R' = \text{Me}$) [IR (CHCl_3) 3500, 1730, 1690, and 1240 cm^{-1} ; NMR (CDCl_3) δ 3.54 (d, $J = 7\text{ Hz}$, $-\text{CH}_2\text{OH}$), 3.64 (s, $-\text{COOCH}_3$), 5.11 (d t, $J_{10\alpha,11} = 3\text{ Hz}$, $J_{10\beta,11} = J_{11,12} = 6\text{ Hz}$, $\text{C}_{11}\text{-H}$)] 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 ($R' = \text{Et}$) yielded the corresponding aldehyde which - without further purification - was converted [dimethyl 2-oxoheptylphosphonate, sodium hydride, tetrahydrofuran (9)] into the enone 7b ($R' = \text{Et}$) [50%; IR (CHCl_3) 1720, 1680, 1620, and 1020 cm^{-1} ; NMR (CDCl_3) δ 0.90 (t, $J = 7\text{ Hz}$, $\text{C}_{20}\text{-H}_3$), 2.28 (t, $J = 7\text{ Hz}$, $-\text{CH}_2\text{COOEt}$), 2.54 (t, $J = 7\text{ Hz}$, $-\text{CO}-\text{CH}_2-$), 2.8 (m, $\text{C}_{12}\text{-H}$), 6.20 (d, $J_{13,14} = 16\text{ Hz}$, $\text{C}_{14}\text{-H}$), 6.70 (d d, $J_{12,13} = 8\text{ Hz}$, $J_{13,14} = 16\text{ Hz}$, $\text{C}_{13}\text{-H}$)].

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} -H₃), 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} -acetoxycarbinol 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 ($R' = Me$).

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