

SYNTHESIS OF 9-AZAPROSTAGLANDIN ANALOGS

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9,11-Dideoxy-9-aza-prostaglandin derivatives are synthesized in nine steps starting from diethyl 7-cyanoheptylidenemalonate.

The interest in novel prostaglandins with specific pharmacological properties has recently led to the synthesis of prostaglandin analogs in which carbon atoms of the 5-membered ring are replaced by hetero atoms. Syntheses of 9-oxa (2), 10-oxa (3), 11-oxa (4), 9,11-dioxa (5), 9-thia (6), 11-thia (7), 8-aza (8) and 8,12-diazaprostaglandins (9) have been described. We now want to report the synthesis of another class of heterocyclic analogs, the 9,11-dideoxy-9-aza-prostaglandin derivatives 8b,c and 9b,c (10).

The crude product from the Michael addition of aziridine (11) to diethyl 7-cyanoheptylidenemalonate 1a (12), was treated with ethyl chloroformate to give urethane 2a [IR 2220, 1720, 1685 cm^{-1} ; NMR (CDCl_3) δ 3.5 (m, $\text{Cl-CH}_2\text{-CH}_2\text{-N-}$), 2.3 (t, $J=7$ Hz, $-\text{CH}_2\text{CN}$)] which was purified by column chromatography over silica gel. Ring closure of 2a by reaction with sodium hydride in benzene at room temperature provided pyrrolidine derivative 3a [IR 2220, 1720, 1690; NMR (CDCl_3) 4.6 (br t, $J=6.5$ Hz, N-CH-R), 3.4 (dd, $J=4$ Hz and 9.5 Hz, $\text{N-CH}_2\text{-}$), 2.35 (t, $J=7$ Hz, $-\text{CH}_2\text{CN}$)] in 80% yield from 1a after purification over silica gel.

Decarbethoxylation of 3a [dimethyl sulfoxide, water, sodium chlo-

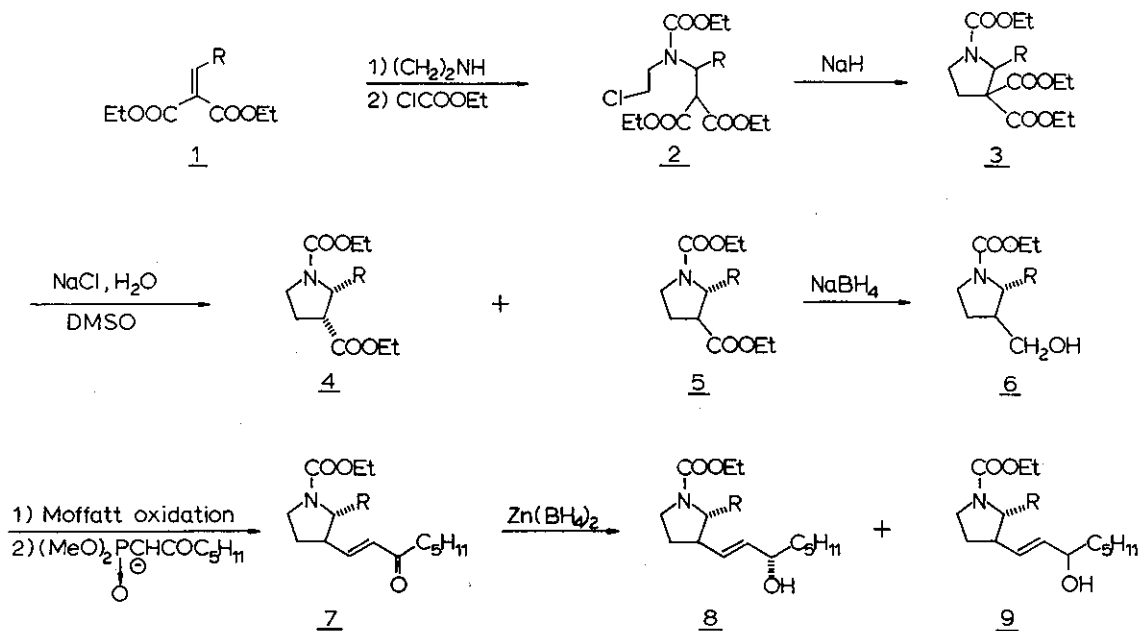
ride; 175° (13)] led to the formation of a mixture of cis-trans isomers 4a and 5a (66%; 1:5) which on epimerization (potassium carbonate, ethanol; reflux) afforded mainly trans isomer 5a [IR 2220, 1720, 1690; NMR (CDCl₃) 2.10 (m, N-CH₂-CH₂-), 2.32 (t, J=7 Hz, -CH₂CN), 2.76 (m, J_{2,3}=3 Hz, >CHCOOEt)].

Reduction of 5a with sodium borohydride in ethanol at room temperature gave the alcohol 6a [90%; IR 3450, 2230, 1690; NMR (CDCl₃) 2.10 (m, N-CH₂-CH₂-), 2.32 (t, J=7 Hz, -CH₂CN), 3.46 (d, J=7 Hz, -CH₂OH)]. Hydrolysis of the nitrile group in 6a (potassium hydroxide, methanol, water; 110°) followed by esterification of the resulting carboxylic acid with diazomethane gave the methyl ester 6b [70%; IR 3450, 1725, 1690; NMR (CDCl₃) 2.0 (m, N-CH₂-CH₂-), 2.28 (t, J=7 Hz, -CH₂COOMe), 3.0 (br, exchangeable in D₂O), 3.46 (d, J=7 Hz, -CH₂OH), 3.63 (s, -COOCH₃)].

The alcohol function in 6b was oxidized [dimethyl sulfoxide, dicyclohexylcarbodiimide, trifluoroacetic acid, pyridine, benzene (14)] to the corresponding aldehyde which - without foregoing purification - was converted [dimethyl 2-oxoheptylphosphonate, sodium hydride, tetrahydrofuran (15)] to the enone 7b [45%; IR 1725, 1690, 1620; NMR (CDCl₃) 0.9 (t, J=6.5 Hz, CH₂-CH₃), 2.31 (t, J=7 Hz, -CH₂COOMe), 2.54 (t, J=7 Hz, -COCH₂-), 2.75 (m, >CH=C=C), 6.14 (d, J_{13,14}=16 Hz, CH=CH-CO), 6.74 (q, J_{12,13}=8 Hz, J_{13,14}=16 Hz, CH=CH-CO)]. Reduction of the C₁₅-carbonyl function in 7b (zinc borohydride, dimethoxy ethane; room temperature) produced a mixture of the C₁₅-epimeric alcohols 8b and 9b [70%; IR 3450, 1720, 1680; NMR (CDCl₃) 0.9 (t, J=6.5 Hz, CH₂CH₃), 2.31 (t, J=7 Hz, -CH₂COOMe), 2.56 (m, >CH-CH=CH), 3.65 (s, COOCH₃), 5.57 (m, -CH=CH-)], which could be separated by chromatography over silica gel (ethyl acetate/cyclohexane 1:1).

Reactions analogous to those described above converted tri-ester 1c (16) into 5c. Regioselective reduction (sodium borohydride, ethanol; room temperature) of the C₁₂-ester function (17) furnished alcohol 6c

[55%; IR 3450, 1725, 1690; NMR (CDCl_3) 2.29 (t, $J=7$ Hz, CH_2COOEt), 3.46 (d, $J=7$ Hz, $-\text{CH}_2\text{OH}$)], which was converted - via the enone 7c - to the mixture of C_{15} - alcohols 8c and 9c (spectra very similar to 8b and 9b).



a $\text{R} = (\text{CH}_2)_6\text{CN}$

b $\text{R} = (\text{CH}_2)_6\text{COOMe}$

c $\text{R} = (\text{CH}_2)_6\text{COOEt}$

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