Communications

A New Synthetic Approach to 8-Aza Analogs of Prostaglandins†

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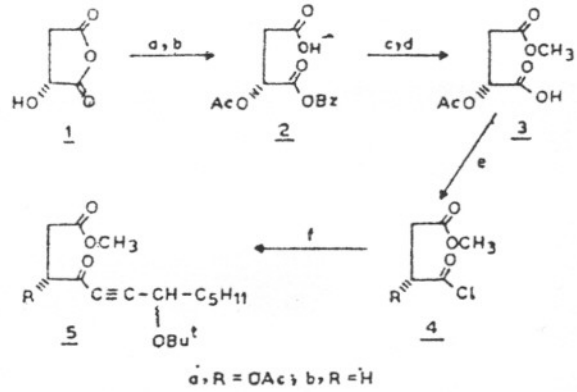
A new synthetic approach to (*dl*)-8-aza-13,14-dihydroprostanoic acid and its corresponding 11-hydroxy derivative is described.

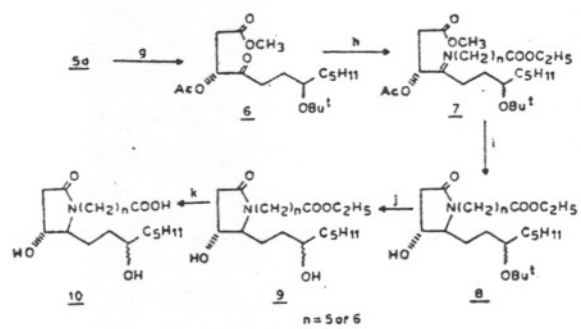
IN continuation of our interest in heterocyclic analogs of prostaglandins[1,2], we report in this communication a new and general approach for the preparation of 8-aza analogs of prostanoids, viz. (*dl*)-8-aza-11-hydroxy-13, 14-dihydroprostanoic acid (**10**) and its corresponding 11-deoxy derivative (**15**). Although this work was completed a few years back[1], the publication was delayed due to our temptation to explore the further possibilities of utilizing the intermediates in the synthesis of related molecules. During this period, quite a few reports have appeared on the synthesis of 8-aza analogs of prostaglandins[3-7] but none of the approaches is as elegant and versatile as the present one.

(*dl*)-8-*Aza* - 11 - *hydroxy* - 13,14- *dihydroprostanoic acid*‡ (**10**) — (*l*)-β-Acetoxymalic acid anhydride, preprepared by the reaction of (*l*)β-hydroxymalic acid anhydride (**1**, Scheme 1) with acetyl chloride, on stirring at 50-60° for 1 hr with benzyl alcohol gave (*l*)β-acetoxy-δ-benzyloxycarbonylpropionic acid (**2**) in about 95% yield; IR (neat) : 1720 1740 and 1760 cm^{-1} (C=O); PMR ($CDCl_3$) : 8.33 (broad *s*, exchangeable with D_2O, 1H), 7.23 (*s*, 5H), 5.40 (*t*, J=6 Hz, 1H), 5.11 (*s*, 2H), 2.81 (*d*, *J*=6 Hz, 2H), 2.01 (*s*, 3H). Esterification of **2** with CH_2N_2 in ether at 0° followed by removal of the benzyl group by hydrogenation (Pd/C, THF) gave α-acetoxy-β-methoxycarbonyl propionic acid (**3**) in ~90% yield, IR (neat) : 1720, 1740 and 1760 cm^{-1} (C=O); PMR : ($CDCl_3$) : 8.88 (broad *s*, eexchangeable with D_2O, 1H), 5.53 (*t*, *J* = 6 Hz, 1H), 3.76 (*s*, 3H), 2.96 (*d*, *J*=6 Hz, 2H), 2.15 (*s*, 3H). The acid chloride (**4a**) obtained by treatment of **3** with oxalyl chloride, was reacted with 3-*t*-butyloxy-1-octynemagnesium bromide and $Cu_2(CN)_2$ in THF to give methyl 3-acetoxy-4-oxo-7-*t*-butyloxy-5-dodecyanoate (**5a**) in 83% yield as a bright brown oil; IR (neat) : 2190 (C≡C), 1760, 1740 and 1680 cm^{-1} (C=O); PMR ($CDCl_3$) : 5.60-5.20 (*m*, 1H), 4.43-3.95 (*m*, 1H), 3.68 (*s*, 3H), 2.80 (*d*, *J* = 7 Hz, 2H), 2.11 (*s*, 3H), 1.96-1.08 (*m*, 17H), 0.91 (*t*, *J* = 6Hz, 3H). The alkynone (**5a**) was reduced catalytically over pd/C (10%) in ethanol to give the alkanone(**6**) (Scheme 2) in quantitative yield ; IR (neat) : 1750 cm^{-1} (broad peak, C=O); PMR ($CDCl_3$) : 5.36 (*t*, *J* = 6 Hz, 1H), 3.95-3.40 (*m*, 4H), 2.76 (*dd*, J = 6 Hz, 2H), 2.10 (*s*, 3H), 1.98-0.58 (*m*, 24H). The alkanone (**6**) on condensation with ethyl 6-aminohexaoate in benzene in the presence of traces of *p*-toluenesulphonic acid gave the corresponding schiff base (**7**), which on treatment with $NaBH_4$ in ethanol at room temperature followed by chromatographic purification of the reaction mixture gave **8** in an overall



a) CH_3COCl ; b) $C_6H_5CH_2OH$; c) CH_2N_2 ; Et_2O ;
d) 10% Pd-C ; H_2 ; T.H.F. ; e) $(COCl)_2$;
f) $CH_3(CH_2)_4-CH(OBu^t)-C\equiv C-MgBr$; $Cu_2(CN)_2$; T.H.F.

SCHEME-1



g) 10% Pd-C ; H_2 ; EtOH ; h) $NH_2(CH_2)_nCOOEt$; C_6H_6 ; TsOH ;
i) $NaBH_4$; EtOH ; j) CF_3COOH ; k) NaOH ; H_2O ; Me_2CO

SCHEME-2

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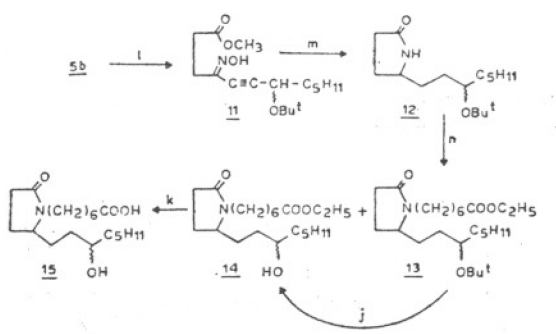
‡Purity of all the compounds was routinely checked by TLC on silica gel G-60 plates. All the compounds have been analysed for C, H and N and gave satisfactory results. PMR spectra were recorded on a Varian A.60D instrument using TMS as internal standard; chemical shifts are given in δ-scale throughout the paper.



i) $NH_2OH.HCl$, $NaHCO_3$, MeOH; m) Raney Ni, H_2, NaOMe, MeOH; n) K, $PhCH_3$, $Br(CH_2)_6COOC_2H_5$

SCHEME-3

yield of 15-20% from **6**, IR (neat) : 3390 (OH), 1730 and 1670 cm^{-1} (C=O); PMR ($CDCl_3$) : 4.11 (*q*, *J* = 7 Hz, 2H), 3.80-3.00 (*m*, 6H; after D_2O exchange, 5H), 2.66-0.55 (*m*, 37H). Treatment of **8** with trifluoroacetic acid at 0° afforded the ester **9** which without further purification was saponified with NaOH (1.1 equiv.) in aq. acetone to give **10**; IR (neat) : 3500-2400 (OH), 1710 and 1670 cm^{-1} (C=O); PMR ($CDCl_3$) : 4.4-3.1 (*m*, 8H; after D_2O exchange, 5H), 2.6-0.5 (*m*, 25H); M^+ for the ethyl ester, *m*/*z* 371.

In a similar manner using methyl 7-aminoheptoate in the place of ethyl 6-aminohexoate for condensation with **6**, (*dl*)-8-aza-11-hydroxy-13, 14-dihydroprostanoic acid was obtained.

(*dl*) 8-*Aza*-13,14-*dihydroprostanoic acid* (**15**)—Addition of β-methoxycarbonylpropionyl chloride (**4b**) to a stirred solution of 3-*t*-butyloxy-1-octynylmagnesium bromide and $Cu_2(CN)_2$ in dry THF gave the alkynone (**5b**) as a brown coloured oil in 80% yield ; IR (neat) : 2210 (C≡C), 1750 and 1680 cm^{-1} (C=O); PMR ($CDCl_3$) : 4.21 (*t*, *J*= 6Hz, 1H), 3.63 (*s*, 3H), 3.00-2.43(*m*, 4H), 2.00-0.66 (*m*, 2OH). **5b** on stirring with $NH_2OH.HCl$/$NaHCO_3$ in methanol for 15 hr at room temperature yielded the corresponding oxime(**11**) (Scheme 3) as an oil in about 95% yield; IR (neat) : 3400 (bonded OH), 2210 (C≡C), 1750 (C=O) and 1610 cm^{-1} (C=N); PMR ($CDCl_3$) : 4.20 (*t*, *J*= 6Hz, 1H), 3.66 (*s*, 3H), 3.00-2.46 (*m*, 4H), 2.00-0.66 (*m*, 2OH). Hydrogenation of **11** in the presence of Raney Ni/$NaOCH_3$ in methanol for 48 hr at 60 psi gave the pyrrolidone **12** in 60% yield; IR (neat) : 3200 (NH) and 1700 cm^{-1} (C=O); PMR ($CDCl_3$) : 8.46 (broad hump, 1H, exchangeable with D_2O), 4.00-3.16 (*m*, 2H), 2.50-0.66 (*m*, 28H); MS : *m*/*z* 269 (M^+), 196 (M^+—C_4H_6NO). Reaction of the K-salt of **12** (prepared by stirring with K-dust in toluene for 2 hr) with ethyl 7-bromoheptoate in refluxing toluene furnished a mixture of **13** and **14** in about 65% yield. This mixture was chromatographed over neutral alumina column, using $CHCl_3$ as eluent, to give **13** and **14**. **13** : IR (neat) : 1750 and 1700 cm^{-1} (C=O); PMR ($CDCl_3$) : 4.15 (*q*, *J* = 7 Hz, 2H), 3.91-3.25 (*m*, 3H), 3.16-0.66 (*m*, 42H).

14 : IR (neat) : 3500 (OH), 1750 and 1680 cm^{-1} (C=O); PMR ($CDCl_3$) : 4.10 (*q*, *J* = 7 Hz, 2H), 3.90-3.20 (*m*, 3H), 3.19-0.66 (*m*, 34H; after D_2O exchange, 33 H). Treatment of **13** with trifluoroacetic acid at 0° for 16 hr gave **14** in 80% yield. **14** on stirring with NaOH (1.1 equiv.) in aq. acetone for 2-3 hr afforded **15** as a thick viscous oil in almost quantitative yield : IR (neat) : 3450-3000 (OH), 1730 and 1680 cm^{-1} (C=O); PMR ($CDCl_3$) : 5.61 (broad hump, exchangeable with D_2O, 2H), 4.00-2.83 (*m*, 4H), 2.66-0.66 (*m*, 29H). **15** on treatment with ethanol in the presence of catalytic amounts of H_2SO_4 gave back the ester (**14**).

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