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SYNTHESIS OF 10-AZAPROSTAGLANDIN E_1

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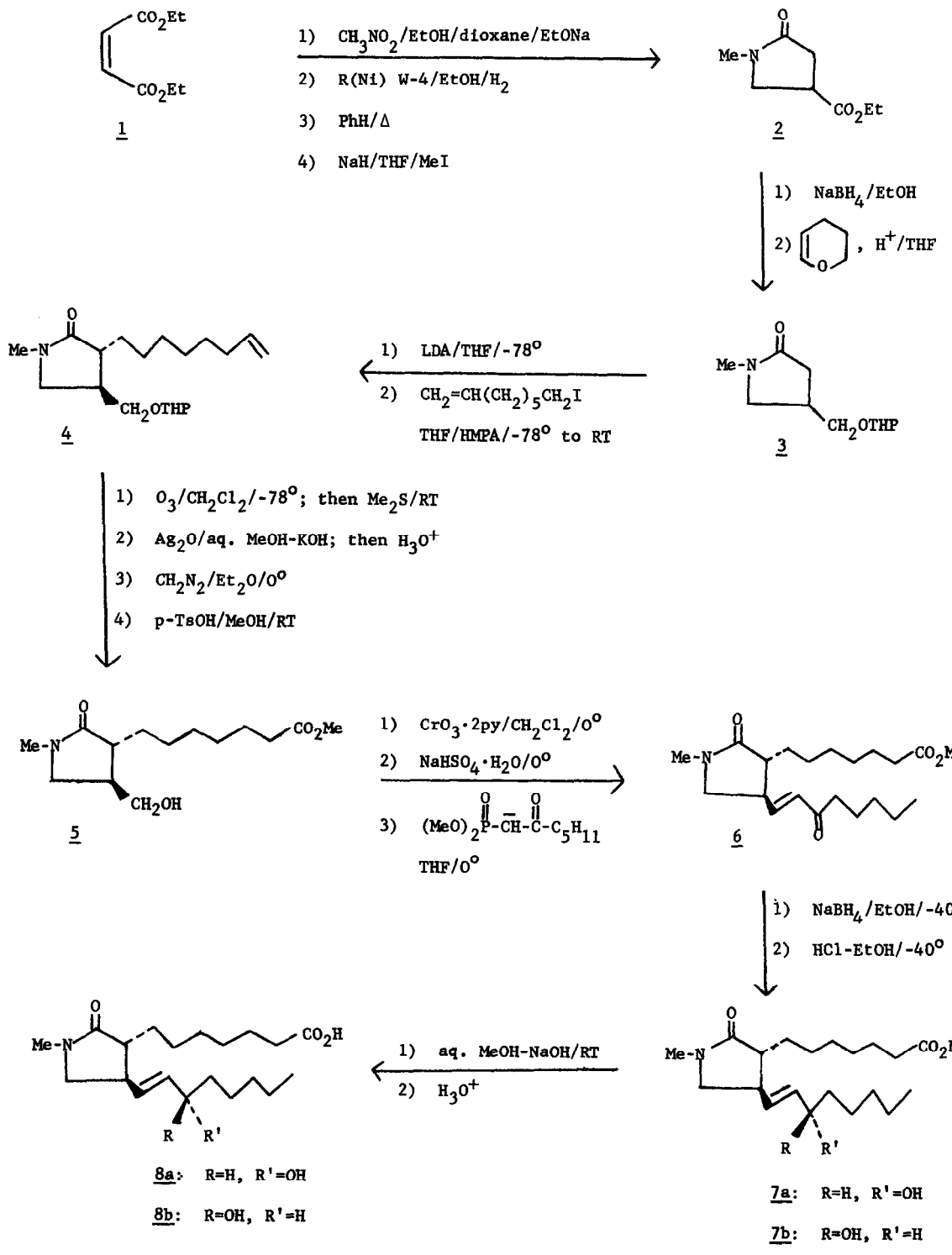
A recent patent publication[1] concerning the synthesis of 11-desoxy-10-azaprostaglandin E_1 prompted us to report an alternative synthetic sequence to 10-aza-PGE_1 8a and 10-aza-15-epi-PGE_1 8b.

Reaction of diethyl maleate 1 with nitromethane in an ethanolic-dioxane solution in the presence of a catalytic amount of sodium ethoxide yielded ethyl 3-carboethoxy-4-nitrobutyrate[2] [49%; ir 1735, 1560 and 1375 cm^{-1}; nmr (CCl_4) δ: 4.80 (m, 2H, $\underline{CH_2}NO_2$), 2.75 (m, 2H, $\underline{CH_2}CO_2Me$), 1.26 (t), and 3.51 (m)]. Catalytic reduction of the nitrodiester in the presence of R(Ni) W-4 in ethanol with hydrogen (47 psi) afforded a mixture of the corresponding lactamester and uncyclized aminodiester. Refluxing this mixture in benzene for 5 hr afforded 4-carboethoxy-2-pyrrolidinone [70%; ir 1725 (broad); nmr (CCl_4) δ: 8.05 (s, $\underline{NH}$), 4.15 (q) and 1.27 (t)].

Reaction of 4-carboethoxy-2-pyrrolidinone with NaH in THF and subsequent methylation with methyl iodide gave the lactamester[3] 2 [88%; ir 1740 and 1690 cm^{-1}; nmr (CCl_4) δ: 4.14 (q), 2.75 (s), 2.45 (d) and 1.27 (t)]. Reduction of (2) with sodium borohydride[4] in ethanol at room temperature for 14 hr afforded 1-methyl-5-hydroxymethyl-2-pyrrolidinone [77%; ir 3390 (broad) and 1675 (broad) cm^{-1}; nmr ($CDCl_3$) δ: 2.85 (s, N-$\underline{CH_3}$)]. Reaction of 1-methyl-5-hydroxymethyl-2-pyrrolidinone with dihydropyran in the presence of a catalytic amount of HCl in CH_2Cl_2 at room temperature gave the tetrahydropyranyllactam 3 [77%; bp 115-20° at 0.05 mm; ir 1695 cm^{-1}; nmr (CCl_4) δ: 4.53 (s, O-$\underline{CH}$-O), 2.75 (s, N-$\underline{CH_3}$)]. Treatment of (3) with lithium diisopropylamide in THF at -78° and subsequent alkylation with 8-iodo-1-octene in THF with one equivalent of HMPA afforded the tetrahydropyranylolefin 4 [75%; ir 1690 and 1645 cm^{-1}; nmr ($CDCl_3$) δ: 5.53-3.74 (m, 1H) 4.83, 5.08 and 5.13 (multiplets, 2H) 4.48 (s, O-$\underline{CH}$-O) and 2.86 (s)].

The desired lactamesteralcohol 5 was obtained from the tetrahydropyranylolefin 4 by utilizing the following sequence of reactions: (1) Ozonolysis of (4) in CH_2Cl_2 at -78° and subsequent re-


CO2Et
CO2Et
1
1) CH3NO2/EtOH/dioxane/EtONa
2) R(Ni) W-4/EtOH/H2
3) PhH/Δ
4) NaH/THF/MeI
Me-N
CO2Et
2
1) NaBH4/EtOH
2) , H+/THF
Me-N
CH2OTHP
3
1) LDA/THF/-78°
2) CH2=CH(CH2)5CH2I
THF/HMPA/-78° to RT
Me-N
CH2OTHP
4
1) O3/CH2Cl2/-78°; then Me2S/RT
2) Ag2O/aq. MeOH-KOH; then H3O+
3) CH2N2/Et2O/0°
4) p-TsOH/MeOH/RT
Me-N
CO2Me
CH2OH
5
1) CrO3·2py/CH2Cl2/0°
2) NaHSO4·H2O/0°
3) (MeO)2P-CH-C-C5H11
THF/0°
Me-N
CO2Me
6
1) NaBH4/EtOH/-40°
2) HCl-EtOH/-40°
Me-N
CO2Me
R R'
7a: R=H, R'=OH
7b: R=OH, R'=H
1) aq. MeOH-NaOH/RT
2) H3O+
Me-N
CO2H
R R'
8a: R=H, R'=OH
8b: R=OH, R'=H

duction of the ozonide with Me_2S at room temperature gave the corresponding lactamtetrahydropyranylaldehyde [75%; ir 1725 and 1690 cm^{-1}; nmr (CCl_4) δ: 9.47 (s, distorted)]; (2) Reaction of the aldehyde with Ag_2O[5] in an aqueous KOH-EtOH solution at room temperature for 2 hr followed by acidification with 10% HCl afforded a tetrahydropyranylacid [94%; nmr ($CDCl_3$) δ: 9.20 (s, $CO_2\underline{H}$), 4.67 (s, O-C$\underline{H}$-O) and 2.87 (s, N-C$\underline{H}_3$)]; (3) Esterification of the acid with CH_2N_2 in Et_2O at 0° gave the corresponding lactamtetrahydropyranylester [83%; ir 1745 and 1690 cm^{-1}; nmr ($CDCl_3$) δ: 4.60 (s, O-C$\underline{H}$-O), 3.68 (s, C$\underline{H}_3$O) and 2.83 (s, N-C$\underline{H}_3$)] ; and (4) Reaction of the lactamtetrahydropyranylester with CH_3OH[6] in the presence of p-TsOH at room temperature for 3.5 hr yielded the desired lactamesteralcohol 5 [98%; ir 3400 (broad), 1675 and 1740 cm^{-1}; nmr ($CDCl_3$) δ: 3.72 (s, C$\underline{H}_3$O) and 2.88 (s, NC$\underline{H}_3$)]. Reaction of (5) with excess Collins reagent[7] in CH_2Cl_2 at 0° for 1.25 hr followed by stirring with powdered $NaHSO_4 \cdot H_2O$ at 0° for 45 min and subsequent chromatography on silica gel G afforded the corresponding lactamesteraldehyde [62%; nmr ($CDCl_3$) δ: 9.73 (d, J = 1 Hz), 3.67 (s) and 2.87 (s)]. Reaction of lactamesteraldehyde with the lithium salt of dimethyl-(2-oxoheptyl)-phosphonate in THF at 0° for 3.5 hr and subsequent chromatography on silica gel G gave the enone 6 [84%; nmr ($CDCl_3$) δ: 6.74 (q, J_{12-13} = 8 Hz, J_{13-14} = 16 Hz) 6.13 (d, J_{13-14} = 16 Hz), 3.60 (s, C$\underline{H}_3$O), 2.80 (s, N-C$\underline{H}_3$) and 0.90 (t, distorted); mass spectrum m/e 265 (M), 334 (M-CH_3O), 236 (M-$(CH_2)_5$-CO_2Me), 234 (M-C_4H_9 and $CH_3CO_2CH_3$), 233 (M-CH_2=CH-$CH_2)_4CO_2CH_3$), 166 (M-CH_2=CH$(CH_2)_4$-CO_2CH_3 and C_4H_9), 151 (M-$(CH_2)_6$-CO_2CH_3 and C_5H_{11}), 124 (M-CH_2=CH-$(CH_2)_4CO_2CH_3$ and $C_5H_{11}C$=O) and 98 (M-CH_2=CH-$(CH_2)_4CO_2CH_3$ and CH=CH-CO-C_5H_{11})].

Reduction of the enone 6 with an ethanolic-sodium borohydride solution at -40° for 4.5 hr followed by destroying the excess $NaBH_4$ with a 10% HCl-EtOH solution at -40° afforded a 1:1 mixture of the C-15 epimeric esteralcohols 7a and 7b [83%; tlc analysis using a 5% methanolic-ether solution indicated two equally intense spots]. Chromatography of the diastereoisomeric mixture 7a and 7b on silica gel G and elution with ether-hexane solutions, gave a faster moving (less polar)[8] diastereoisomer 7b[9] [mp 50-51°; ir 3450 (broad), 1745 and 1690 cm^{-1}; nmr (CCl_4) δ: 5.47-5.63 (m), 3.62 (s, OC$\underline{H}_3$), 2.71 (s, NC$\underline{H}_3$) and 0.90 (t, distorted); mass spectrum m/e 367 (M), 350 (M-OH), 336 (M-CH_3O), 296 (M-C_5H_{11}), 264 (M-C_5H_{11} and CH_3OH), 236 (M-$CH_3CO_2CH_3$ and C_4H_9), 225 (M-CH_2=CH-$(CH_2)_4$-CO_2CH_3, 182 (M-$(CH_2)_6$-CO_2CH_3 and C_3H_7), 168 (M-CH_2=CH-$(CH_2)_4$-CO_2CH_3 and C_4H_9), and 154 (M-CH_2=CH-$(CH_2)_4$-CO_2CH_3 and C_5H_{11})] and a slower moving (more polar) diastereoisomer 7a [mp 54-54.5°; the ir, nmr and mass spectrum of 7a were essentially identical to that of 7b].

Reaction of the esteralcohol 7a with an aqueous methanolic-sodium hydroxide solution at room temperature for 20 hr followed by acidification afforded 10-aza-11-desoxy-PGE_1 8a [mp 123-24°; ir 1735 and 1685 cm^{-1}; nmr ($CDCl_3$) δ: 6.10 (s, broad, 2H, CO_2H and OH), 5.40-5.73 (m), 2.85 (s) and 0.90 (t, distorted); mass spectrum m/e 353 (M), 336 (M-OH), 335 (M-H_2O), 318 (M-H_2O and OH), 282 (M-C_5H_{11}), 264 (M-C_5H_{11} and H_2O), 225 (M-CH_2-CH-$(CH_2)_4$-CO_2H), 224 (M-$(CH_2)_6$-CO_2H), 208 (M-CH_2=CH-$(CH_2)_4$-CO_2H and OH), 150 (M-$(CH_2)_6$-CO_2H, OH and C_4H_9) and 98 (M-CH_2=CH$(CH_2)_4$-CO_2H and CH=CH-$CHOHC_5H_{11}$)].

Saponification of the esteralcohol 7b with an aqueous methanolic-sodium hydroxide solution at room temperature and subsequent acidification yielded 10-aza-11-desoxy-15-epi-PGE_1 8b [mp 83-84°; ir 1725 and 1685 cm^{-1}; mass spectrum and nmr of 8b were very similar to 8a].

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8. The less polar compound was tentatively assigned to the 15β-epimer 7b in analogy with the characteristic tlc behavior of methyl 11-desoxy-PGE_1 and methyl 11-desoxy-15-epi-PGE_1.
9. Elemental analysis were consistent for the structures proposed.

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