Synthetic Approaches to 10-Azaprostaglandins

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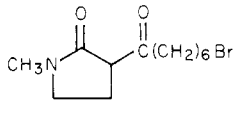
The synthesis of 10-aza-11-deoxyprostaglandin E_1 (**12**) is reported. A second synthetic route to the 10-azaprostaglandin E_2 analogues **21** is also discussed.

The 10-azaprostaglandins have been shown to be physiologically[2] active. Recently in a communication we[3] and Reuschling and co-workers[4] described the synthesis of 10-azaprostaglandin E_1. Herein we fully disclose our findings and also present a second synthetic approach to the 10-azaprostaglandin E series that allows ready synthesis of analogues containing modified C-7 side chains from a common synthon.

The protected lactam alcohol **4** (Scheme I) could be envisioned as an ideal starting material for synthesizing 10-azaprostaglandin E_1 **12**. The synthesis of **4** and the subsequent conversion of this synthon into 10-azaprostaglandin E_1 was realized as outlined below.

Reaction of dimethyl itaconate[5] (**1**) and methylamine afforded a 54% yield of the lactam ester **2**. Preferential reduction of the ester moiety was effected with excess $NaBH_4$[6] to afford a 78% yield of the lactam alcohol **3**. Reaction of **3** with dihydropyran in the presence of a catalytic amount of HCl gave the tetrahydropyranyl lactam **4** in 76% yield.

At this point, it was anticipated that the C-7 side chain containing an intact ester moiety could be introduced at C-3 by alkylation with methyl 7-bromoheptanoate. A model study with 1-methyl-2-pyrrolidinone was undertaken to obtain the optimum reaction conditions for the proposed alkylation. Surprisingly reaction of the lithium salt of 1-methyl-2-pyrrolidinone with methyl 7-bromoheptanoate (−78 to +20 °C) in THF in the presence of 1 equiv of HMPA did not afford the C-alkylated product but gave instead the keto lactam **13** resulting from acylation

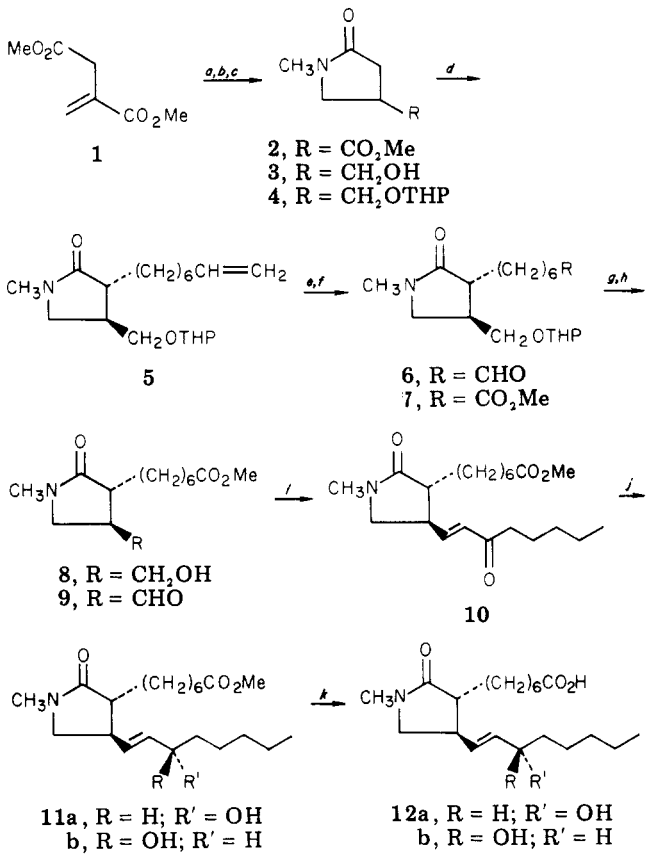


13

at C-3. The constitution of **13** was readily confirmed from the mass spectrum [*m/e* M (289, 291), 141 (M − Br-$(CH_2)_3CH{=}CH_2$), 98 (M − $Br(CH_2)_6C{=}O$)] and the absence of a methyl ester resonance peak in the NMR spectrum.

The acylation problem was circumvented by adopting a strategy to introduce a side chain that could be degraded into the desired heptanoic acid moiety. An ideal reagent for this approach is 8-iodo-1-octene. Thus alkylation of the lithium salt of **4** with 8-iodo-1-octene at −78 °C in the presence of 1 equiv of HMPA afforded a 75% yield of the trans olefin **5**. The trans stereochemistry should result as

Scheme I



[a] CH_3NH_2. [b] $NaBH_4$, EtOH. [c] Dihydropyran, CH_2Cl_2, 12 N HCl. [d] $(Me_2CH)_2NH$, THF, *n*-BuLi; $I(CH_2)_6CH{=}CH_2$, HMPA, −78 to +25 °C. [e] O_3, CH_2Cl_2, −78 °C; Me_2S. [f] $AgNO_3$, aqueous KOH; H^+, CH_2N_2. [g] MeOH, *p*-TsOH. [h] $CrO_3{\cdot}2py$, CH_2Cl_2. [i] $(MeO)_2POCHCOC_5H_{11}$, THF, 0 °C. [j] $NaBH_4$, EtOH, −40 °C; 10% HCl-EtOH, −40 °C. [k] Aqueous MeOH-NaOH; H_3O^+.

expected from alkylation occurring from the opposite side of the bulky C-4 side chain. The trans stereochemistry is also indicated from the fact that treatment of **5** with 1 equiv of LDA at −78 °C afforded a compound whose R_f value was identical with that of **5** derived from direct alkylation of **4** and from the fact that hydrolysis of **5** afforded an alcohol whose R_f value was also identical with the R_f value of the alcohol derived from **5** after treatment with LDA.

Ozonolysis of **5** in CH_2Cl_2 at −78 °C and concomitant reduction of the ozonide with Me_2S afforded the aldehyde **6** in 76% yield. Oxidation of aldehyde **6** with Ag_2O[7] in an aqueous KOH–EtOH solution and subsequent esterification of the resulting acid with CH_2N_2 gave a 74% yield of the tetrahydropyranyl ester **7**. Cleavage of the protecting

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group was effected by reaction of **7** with methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid to afford the lactam alcohol **8** in 97% yield.

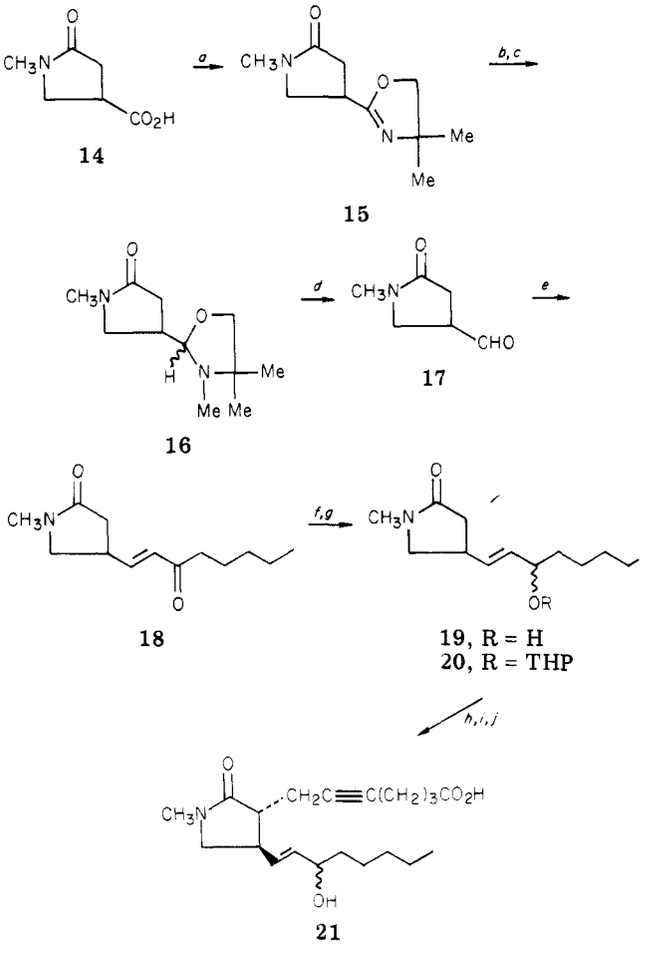
Oxidation of **8** with Collin's reagent[8] in CH_2Cl_2 at 0 °C gave a 62% yield of the aldehyde **9**; subsequent reaction of **9** with the lithium salt of dimethyl (2-oxoheptyl)-phosphonate at 0 °C in THF afforded the enone **10** in 84% yield. Reduction of **10** with $NaBH_4$ at −40 °C gave a 1:1 mixture of the C-15 epimeric alcohols **11a** and **11b**. The diastereoisomers were separated by column chromatography on silica gel to afford a faster moving (less polar) diastereoisomer **11b** (mp 50–51 °C) and a slower moving (more polar) diastereoisomer **11a** (mp 54–54.5 °C). TLC analysis indicated two distinct compounds. The IR, NMR, and mass spectra of **11a** and **11b** were essentially identical. The less polar compound **11b** was assigned to the 15β epimer and the more polar compound **11a** was assigned to the 15α epimer in analogy with the characteristic TLC behavior of 15α- and 15β-prostaglandins E_1. Saponification of **11a** and **11b** with an aqueous methanolic sodium hydroxide solution followed by acidification and subsequent chromatography afforded an 89% yield of 10-azaprostaglandin E_1 (**12a**) (mp 123–124 °C) and an 87% yield of 15-epi-10-azaprostaglandin E_1 (**12b**) (mp 83–84 °C).

A second feasible route to the 10-azaprostaglandin E series might be through the tetrahydropyranyl lactam **20** (Scheme II). This key synthon could be used readily to synthesize various 10-azaprostaglandin E analogues containing modified top-side chains. The lactam alcohol **3**, could serve as a precursor for the construction of synthon **20**. However, Collin's oxidation of **3** gave poor yields of the desired aldehyde **17**. This was attributed mainly to the water solubility of the lactam aldehyde. A nonaqueous isolation procedure following Collin's oxidation, that is, direct column chromatography of the concentrated reaction solution, also proved difficult on a large scale. If the desired aldehyde **17** is to be obtained in an appreciable yield, an aqueous workup must be avoided. Thus we envisioned the oxazolidine **16**, which contains a protected aldehyde moiety, as an ideal precursor to **17**, since it might be expected that the oxazolidino moiety could be cleaved with a minimal amount of water, thereby circumventing the aqueous solubility problem. The synthesis of the oxazolidine **16** and its utilization in the synthesis of a 10-azaprostaglandin E_2 analogue **21** is depicted in Scheme II.

Saponification of the lactam ester **2** afforded the acid **14** in 91% yield. Reaction of **14** and 2-amino-2-methylpropanol in a toluene–HMPA solution with concomitant removal of H_2O gave a 54% yield of the oxazoline **15**.[9] Subsequent N-alkylation with methyl iodide and reduction of the resulting oxazolinium iodide with $NaBH_4$[10,11] afforded the oxazolidine **16** in 65% yield. Hydrolysis of the oxazolidine **16** with an aqueous trifluoroacetic acid–tetrahydrofuran solution at room temperature and subsequent chromatography on silica gel, on an ion-exchange resin (Dowex 50-W), and finally on silica gel afforded a 58% yield of the aldehyde **17**. Reaction of **17** with the lithium salt of dimethyl (2-oxoheptyl)phosphonate gave the enone **18** in 70% yield after chromatography.

Reduction of enone **18** with an ethanolic sodium borohydride solution at −40 °C afforded a mixture of the desired lactam alcohols **19** and the dihydro alcohols derived from 1,4-hydride addition and subsequent reduction of the corresponding saturated ketone. 1,4-Reduction was evident from the mass spectrum which displayed molecular ions at *m/e* 225 and 227 and from the integration of the vinyl region in the NMR spectrum. On the basis of the integrated vinyl region, it was determined that approximately 40% 1,4-addition had occurred during reduction. These compounds could not be separated by column chromatography. The 1,4-addition problem could be circumvented, however, by employing $LiEt_3BH$ as the reducing agent. Thus reaction of enone **18** with $LiEt_3BH$ in THF at −78 °C gave the alcohols **19** in 75% yield after chromatography. The constitution of **19** was consistent with the mass spectrum [*m/e* 225 (M), 208 (M − OH), 196 (M − CH_2CH_3), 154 (M − C_5H_{11}), 98 (M − CH=CHCHOHC_5H_{11})] and microanalysis. TLC analysis showed the diastereoisomeric mixture of alcohols **19** as one distinct spot in a variety of solvent systems. Reaction of the alcohols **19** and dihydropyran in CH_2Cl_2 in the presence of *p*-toluenesulfonic acid afforded a 71% yield of the tetrahydropyranyl lactams **20** after chromatography. Reaction of 2 equiv of the lithium salt of **20** with methyl 7-bromo-5-heptynoate in THF at −78 °C and then room temperature overnight, followed by saponification of the resulting lactam esters and subsequent cleavage of the tetrahydropyranyl moiety with an aqueous acetic acid–

Scheme II



[a] $NH_2CMe_2CH_2OH$, HMPA, $PhCH_3$. [b] CH_3I, CH_3NO_2. [c] $NaBH_4$, MeOH. [d] Aqueous CF_3CO_2H-THF. [e] $(MeO)_2POCHCOC_5H_{11}$, THF, 0 °C. [f] $LiEt_3BH$, THF, −78 °C. [g] Dihydropyran, CH_2Cl_2, *p*-TsOH. [h] $(Me_2CH)_2NH$, THF, *n*-BuLi; $BrCH_2C{\equiv}C(CH_2)_3CO_2Me$. [i] Aqueous MeOH-NaOH; H^+. [j] Aqueous HOAc-THF.

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(9) For a review of oxazoline chemistry see: J. A. Frump, *Chem. Rev.*, 71, 483 (1971); A. I. Meyers, "Heterocycles in Organic Synthesis", Wiley, New York, 1974.

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THF solution, gave the lactam acids **21** in 32% yield after chromatography. It is anticipated that alkylation of **20** should occur from the opposite side of the bulk C-8 side chain. The presence of 2 equiv of base in the reaction medium would also ensure the depicted trans stereochemistry in **21** via epimerization of the C-8 position. TLC analysis in a variety of solvent systems showed the lactam acids **21** as an elongated spot.

Experimental Section

Methyl 5-Oxo-3-pyrrolidinecarboxylate (2). Dimethyl itaconate (**1**) (204 g, 1.29 mol) in 50 mL of methanol was added with stirring over a 1-h period to monomethylamine (40.2 g, 1.29 mol) in 150 mL of methanol, while the reaction temperature was kept at 5–10 °C. The reaction mixture was stirred at room temperature for 48 h and concentrated in vacuo. Distillation of the residue afforded 109.7 g (54%) of the lactam ester **2**: NMR (CCl_4) δ 2.45 (d, 2 H), 2.75 (s, 3 H), 2.95–3.60 (m, 3 H), 3.68 (s, 3 H); IR (neat) 1690, 1740 cm^{-1}.

4-(Hydroxymethyl)-1-methyl-2-pyrrolidinone (3). $NaBH_4$ (26.6 g, 0.70 mol) was added in small portions over a 7.5-h period to the lactam ester **2** (11.0 g, 0.070 mol) in 300 mL of ethanol. The resulting reaction mixture was stirred at room temperature for 14 h. Water (20 mL) was added to the reaction mixture and the heterogeneous mixture was filtered through Celite 545 with suction. The filtrate was concentrated on a rotary evaporator to afford a solid residue which was suspended in 800 mL of $CHCl_3$, and the resulting mixture was stirred overnight. The $CHCl_3$ solution was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 9.0 g of an oil. Distillation of the oil yielded 7.0 g (78%) of the lactam alcohol **3**: bp 122 °C (0.02 mm); NMR ($CDCl_3$) δ 2.05–2.80 (m, 3 H), 2.85 (s, 3 H), 3.12–3.70 (m, 4 H), 4.92 (t, 1 H, OH, J = 5 Hz); IR (neat) 3390 (br), 1675 (br) cm^{-1}. Anal. Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.84; H, 8.37; N, 10.52.

3-[[(Tetrahydro-2*H*-pyran-2-yl)oxy]methyl]-1-methyl-5-oxopyrrolidine (4). To the lactam alcohol **3** (4.45 g, 0.0345 mol) and dihydropyran (3.48 g, 0.0414 mol) dissolved in 15 mL of CH_2Cl_2 was added 3 drops of 12 N HCl. The resulting reaction mixture was stirred for 5.5 h at room temperature, washed with 6 mL of a 10% $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford an oil. Distillation of the oil gave 5.6 g (76%) of the tetrahydropyran **4**: bp 120 °C (0.1 mm); NMR (CCl_4) δ 1.20–1.87 (m, 6 H), 1.97–2.70 (m, 3 H), 2.75 (s, 3 H), 3.0–3.96 (m, 6 H), 4.53 (m, br, 1 H, OCHO); IR (neat) 1695 cm^{-1}.

4-(7-Octenyl)-3-[[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl]-1-methyl-5-oxopyrrolidine (5). A hexane solution of 2.5 M *n*-BuLi (5.63 mL, 0.0141 mol) was added with a syringe to diisopropylamine (2.85 g, 0.0282 mol) in 15 mL of dry THF at 0 °C under N_2. The reaction mixture was cooled to −78 °C and stirring was continued for 30 min at −78 °C. The tetrahydropyran **4** (3.0 g, 0.0141 mol) in 17 mL of THF was added over a 25-min period and the reaction mixture was stirred for an additional 30 min at −78 °C. 8-Iodo-1-octene (3.34 g, 0.0141 mol) and HMPA (2.52 g, 0.0141 mol) in 20 mL of THF were added over a 30-min period at −78 °C. The reaction mixture was stirred at −78 °C for 30 min and then was allowed to warm to −25 °C. The reaction mixture was stirred at −25 °C for 25 min, allowed to warm to room temperature, and stirred for 30 min.

The reaction mixture was poured into 125 mL of H_2O and extracted with three 100-mL portions of $CHCl_3$. The $CHCl_3$ extracts were combined, washed with two 100-mL portions of H_2O, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a light yellow oil. The oil was chromatographed on silica gel G. Elution with ether–hexane solutions gave 3.4 g (75%) of the olefin **5**: NMR ($CDCl_3$) δ 1.06–1.75 (m) and 1.80–2.63 (m) (2 OH), 2.86 (s, 3 H), 3.0–4.0 (m, 6 H), 4.61 (m, br, 1 H, OCHO), 4.83–5.17 (m, 2 H), 5.53–6.23 (m, 1 H); IR (neat) 1690, 1645 cm^{-1}. Anal. Calcd for $C_{19}H_{33}NO_3$: C, 70.55; H, 10.28; N, 4.33. Found: C, 70.18; H, 10.38; N, 4.26.

4-(6-Formylhexyl)-3-[[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl]-1-methyl-5-oxopyrrolidine (6). The olefin **5** (2.1 g, 0.00650 mol) dissolved in 50 mL of CH_2Cl_2 was cooled to −78 °C. Ozone was passed through the solution until an excess of ozone was detected with a saturated KI solution. N_2 was then passed through the solution to remove excess O_3. Dimethyl sulfide (10 mL) was added and the reaction mixture was allowed to warm to room temperature and stand overnight. Concentration of the reaction mixture in vacuo afforded an oil. TLC analysis indicated the presence of unreduced ozonide. DMS (6 g) was added to the oil in 20 mL of CH_2Cl_2 and the reaction mixture was stirred at room temperature for 22 h and concentrated in vacuo. The residue was chromatographed on silica gel G. Elution with ether–hexane solutions gave 1.6 g (76%) of the aldehyde **6**: NMR ($CDCl_3$) δ 1.0–2.0 (m, 16 H), 2.0–2.60 (m, 4 H), 2.85 (s, 3 H), 3.08–4.10 (m, 6 H), 4.60 (m, OCHO, 1 H), 9.80 (d, 1 H); IR (neat) 1725, 1690 cm^{-1}.

Methyl 7-[3-(Hydroxymethyl)-1-methyl-5-oxo-4-pyrrolidinyl]heptanoate (8). $AgNO_3$ (9.13 g, 0.0538 mol) in 11.5 mL of H_2O was added to the aldehyde **6** (7.5 g, 0.0231 mol) in 115 mL of ethanol at room temperature. KOH (6.90 g, 0.123 mol) in 115 mL of water was then added over a 30-min period and the resulting reaction mixture was stirred for an additional 3 h. The silver salts were filtered by gravity and the residue was washed with H_2O. The filtrate was extracted with two 100-mL portions of $CHCl_3$. The aqueous layer was acidified (pH 2) with 12 N HCl, extracted with three 150-mL portions of $CHCl_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 7.1 g (90%) of the corresponding acid: NMR ($CDCl_3$) δ 9.20 (s, br, CO_2H), 4.40–4.72 (m, OCHO), 2.88 (s, NCH_3).

An ether solution of CH_2N_2 was added to the acid (7.05 g, 0.0206 mol) in 50 mL of ether at 0 °C until a yellow color persisted, and stirring was continued for an additional 15 min. The reaction mixture was diluted with 125 mL of ether and washed with 75 mL of a 10% $NaHCO_3$ solution and 50 mL of H_2O. The water and $NaHCO_3$ washings were combined and extracted with 200 mL of a 50% Et_2O–CH_2Cl_2 solution and the organic solution was washed with 50 mL of H_2O. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 5.4 g (74%) of the crude tetrahydropyranyl ester **7**: NMR ($CDCl_3$) δ 1.0–2.5 (m, 20 H), 2.83 (s, 3 H), 3.0–3.40 (m) and 3.68 (s, OCH_3) (9 H), 4.65 (m, 1 H); IR (neat) 1745, 1690 cm^{-1}.

p-Toluenesulfonic acid (332 mg) was added to the tetrahydropyranyl ester **7** (5.0 g, 0.0141 mol) in 100 mL of absolute methanol and the resulting reaction mixture was heated at 45 °C with stirring for 4 h. Solid $NaHCO_3$ (4.54 g) was added and stirring was continued for 0.5 h. The solvent was removed in vacuo and the residue was dissolved in 300 mL of CH_2Cl_2. The organic solution was extracted with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an oil. The oil was passed through a short silica gel column to afford 3.7 g (97%) of the ester alcohol **8**: NMR ($CDCl_3$) δ 1.0–2.0 (m, 10 H), 2.05–2.60 (m, 4 H), 2.88 (s, 3 H), 3.0–4.0 (m) and 3.72 (s, OCH_3) (8 H); IR (neat) 3400 (br), 1740, 1675 cm^{-1}. Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.21; H, 9.47; N, 5.07.

Methyl 7-(3-Formyl-1-methyl-5-oxo-4-pyrrolidinyl)heptanoate (9). The ester alcohol **8** (3.41 g, 0.0126 mol) in 820 mL of dry CH_2Cl_2 was cooled to 0 °C under N_2. Collin's reagent, CrO_3·2py (19.48, 0.0755 mol), in 400 mL of CH_2Cl_2 was added all at once and stirring was continued at 0 °C for 1.5 h. Powdered $NaHSO_4$·H_2O (40 g) was then added and the reaction mixture was stirred for an additional 10 min. The reaction solution was decanted and the residue washed with CH_2Cl_2. The organic solutions were combined, extracted with two 500-mL portions of 5% HCl, and consecutively washed with 600-mL portions of brine, 5% $NaHCO_3$, and brine. The organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 3.4 g of a brown oil. The oil was chromatographed on 25 g of silica gel G. Elution with ether–hexane and methanol–ether solutions gave 2.1 g (62%) of the aldehyde **9**: NMR ($CDCl_3$) δ 1.07–1.93 (m) and 2.13–2.50 (m) (14 H), 2.06–3.57 (m) and 2.87 (s, NCH_3) (5 H), 3.67 (s, 3 H), 9.73 (d, 1 H, J = 1 Hz). The aldehyde was not characterized further and was committed directly to the Wadsworth–Emmons reaction.

(*E*)-Methyl 7-[3-(3-Oxo-1-octenyl)-1-methyl-5-oxo-4-pyrrolidinyl]heptanoate (10). A hexane solution of 2.5 M *n*-BuLi (3.12 mL, 0.00781 mol) was added with a syringe to dimethyl (2-oxoheptyl)phosphonate (1.73 g, 0.00780 mol) in 25 mL of THF at 0 °C under N_2 and stirring was continued for 20 min. The aldehyde **9** (2.1 g, 0.00781 mol) in 40 mL of THF was added, and the reaction mixture was stirred at 0 °C for an additional 3.5 h. The reaction mixture was diluted with 200 mL of ice–H_2O

and extracted with three 150-mL portions of CH_2Cl_2. The organic solutions were combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 2.8 g of an oil. The oil was chromatographed on silica gel G (9:1). Elution with ether–hexane and methanol–ether solutions afforded 2.4 g (84%) of the enone **10**: NMR (CCl_4) δ 0.90 (t, distorted) and 1.07–1.93 (m) (19 H), 2.06–2.67 (m, 6 H), 2.80 (s, 3 H), 2.87–3.43 (m, 2 H), 3.60 (s, 3 H), 6.13 (d, 1 H, $J_{13,14}$ = 16 Hz), 6.74 (dd, 1 H, $J_{12,13}$ = 8 Hz, $J_{13,14}$ = 16 Hz); mass spectrum, m/e 365 (M). Anal. Calcd for $C_{21}H_{35}NO_4$: C, 69.01; H, 9.65; N, 3.83. Found: C, 68.72; H, 9.47; N, 3.69.

(*E*)-Methyl 7-[3-(3-Hydroxy-1-octenyl)-1-methyl-5-oxo-4-pyrrolidinyl]heptanoates (11a and 11b). $NaBH_4$ (0.75 g, 0.0197 mol) was placed in the reaction vessel and the vessel was cooled to −40 °C under N_2. Dry ethanol (175 mL) was added to obtain a clear ethanolic $NaBH_4$ solution at −40 °C. The enone **10** (2.40 g, 0.00658 mol) in 50 mL of absolute ethanol was added at once and the reaction mixture was stirred for 4.5 h at −40 °C. Excess $NaBH_4$ was destroyed with a 10% ethanolic HCl solution at −40 °C. The resulting suspension was filtered with suction, and the ethanolic filtrate was concentrated on a rotary evaporator to afford a slurry. The residual slurry was dissolved in 150 mL of $CHCl_3$ and was washed with 75 mL of H_2O. The H_2O layer was then extracted with four 100-mL portions of $CHCl_3$, and the combined $CHCl_3$ extracts were washed with 150 mL of brine. The organic solutions were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 2.7 g of a viscous oil. TLC analysis of the crude product revealed a 1:1 epimeric mixture. The crude ester alcohols were chromatographed on silica gel G (50 g). Elution with ether–hexane and methanol–ether solutions gave 700 mg of a faster moving (less polar) diastereoisomer **11b** [mp 50–51 °C (MeOH–Et_2O); NMR (CCl_4) δ 0.91 (t, distorted, 3 H), 1.07–1.77 (m, 18 H), 1.90–2.60 (m, 5 H), 2.77 (s, 3 H), 2.83–3.47 (m, 2 H), 3.62 (s, 3 H), 3.75–4.20 (m, 1 H), 5.47–5.63 (m, 2 H); IR (KBr) 3450 (br), 1745, 1690 cm^{-1}; mass spectrum, m/e 367 (M). Anal. Calcd for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 68.50; H, 9.98; N, 3.78] and 1.3 g of a diastereoisomeric mixture of **11b** and **11a** which was enriched in **11a** as shown by TLC analysis. The total yield of **11a** and **11b** was 83%.

The 1.3-g mixture was chromatographed on silica gel, and elution with ether–hexane and ether–methanol solutions afforded 1.0 g of the more polar isomer **11a**: mp 54–54.5 °C (MeOH–Et_2O); NMR (CCl_4) δ 0.92 (t, distorted, 3 H), 1.10–1.77 (m, 18 H), 1.92–2.60 (m, 5 H), 2.78 (s, 3 H), 2.83–3.47 (m, 2 H), 3.62 (s, 3 H), 3.85–4.30 (m, 1 H), 5.45–5.72 (m, 2 H); IR (KBr) 3450 (br), 1745, 1690 cm^{-1}; mass spectrum, m/e 367 (M). Anal. Calcd for $C_{21}H_{37}NO_4$: C, 68.63; H, 10.15; N, 3.81. Found: C, 68.58; H, 9.90; N, 3.79.

(*E*)-7-[3-(3β-Hydroxy-1-octenyl)-1-methyl-5-oxo-4-pyrrolidinyl]heptanoic Acid (12b). The ester alcohol **11b** (0.18 g, 0.000490 mol) was dissolved in 2.4 mL of methanol. An aqueous sodium hydroxide solution [NaOH (0.02 g, 0.000540 mol) and 0.9 mL of H_2O] was added to the above solution, and the resulting reaction mixture was stirred at room temperature for 22 h. The reaction mixture was poured into 20 mL of H_2O and extracted with two 30-mL portions of ether. The aqueous layer was acidified (pH 2) with 12 N HCl and extracted with three 30-mL portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 150 mg (87%) of 15β-10-azaprostaglandin E_1 **12b**: mp 83–84 °C (triturated, MeOH–Et_2O); NMR (CCl_4) δ 0.91 (t, distorted) and 1.03–1.97 (m) (21 H), 2.08–2.53 (m), 2.84 (s), 2.95–3.60 (m), and 3.72–4.28 (m) (10 H), 5.41–5.75 (m, 2 H), 6.33 (s, br, 2 H, CO_2H and OH); IR (KBr) 1685, 1735 cm^{-1}; mass spectrum, m/e 353 (M). Anal. Calcd for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96. Found: C, 67.86; H, 10.08; N, 3.92.

(*E*)-7-[3-(3α-Hydroxy-1-octenyl)-1-methyl-5-oxo-4-pyrrolidinyl]heptanoic Acid (12a). The ester alcohol **11a** (0.20 g, 0.000545 mol) was dissolved in 2.7 mL of methanol. An aqueous sodium hydroxide solution [NaOH (0.024 g, 0.000600 mol) and 1.0 mL of H_2O] was added to the above solution, and the resulting reaction mixture was stirred at room temperature for 24 h. The reaction mixture was poured into 20 mL of H_2O and extracted with two 30-mL portions of Et_2O. The aqueous layer was acidified with 12 N HCl and extracted with three 30-mL portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 170 mg (89%) of 15α-10-azaprostaglandin E_1 **12a**: mp 123–124 °C (triturated, MeOH–Et_2O); NMR ($CDCl_3$) δ 0.90 (t, distorted) and 1.05–1.95 (m) (21 H), 1.98–2.53 (m), 2.85 (s), 2.95–3.60 (m), and 3.79–4.30 (m) (10 H), 5.40–5.73 (m, 2 H), 6.10 (s, br, 2 H, CO_2H and OH); IR (KBr) 1685, 1735 cm^{-1}; mass spectrum, m/e 353 (M). Anal. Calcd for $C_{20}H_{35}NO_4$: C, 67.95; H, 9.98; N, 3.96. Found: C, 67.66; H, 9.78; N, 3.89.

1-Methyl-5-oxo-3-pyrrolidinecarboxylic Acid (14). An aqueous methanolic sodium hydroxide solution [NaOH (88 g, 2.2 mol), MeOH (300 mL), and H_2O (100 mL)] was added to the lactam ester **2** (170 g, 1.08 mol). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was acidified, the solvent was removed in vacuo, and the residue was extracted with $CHCl_3$. The organic solution was dried over $MgSO_4$ and concentrated in vacuo to afford 140 g (91%) of the lactam acid **14**. The NMR spectrum of the ester obtained from the reaction of **14** and CH_2N_2 was identical with the NMR spectrum of the lactam ester **2**.

2-(1-Methyl-5-oxo-3-pyrrolidinyl)-4,4-dimethyl-2-oxazoline (15). The lactam acid **14** (55.0 g, 0.385 mol) in 190 mL of HMPA was added to 2-amino-2-methylpropanol (68.6 g, 0.771 mol) in 460 mL of toluene, and the resulting reaction mixture was refluxed (Dean–Stark trap) for 5 days. After cooling, the reaction mixture was concentrated on a rotary evaporator. Removal of the solvents and unreacted amino alcohol was effected by distillations at 12 and 0.15 mm, respectively. The resulting residue was distilled twice to afford 40.7 g (54%) of the oxazoline **15**: bp 110 °C (0.08 mm); NMR (CCl_4) δ 1.20 (s, 6 H), 2.44 (d, 2 H, J = 7.5 Hz), 2.75 (s, 3 H), 2.85–3.70 (m, 3 H), 3.88 (s, 2 H); IR (neat) 1710, 1675 cm^{-1}. Anal. Calcd for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 60.79; H, 8.01; N, 14.11.

2-(1-Methyl-5-oxo-3-pyrrolidinyl)-3,4,4-trimethyl-2-oxazolidines (16). Methyl iodide (50.5 g, 0.356 mol) was added to the oxazoline **15** (34.9 g, 0.178 mol) in 80 mL of dry CH_3NO_2, and the reaction mixture was heated at 70 °C for 24 h. Methyl iodide (25.3 g) was added, and heating at 70 °C was continued for an additional 4 h. The reaction mixture was cooled to room temperature, concentrated in vacuo, and heated at 0.1 mm to afford 60.1 g (100%) of the oxazolinium iodide: NMR (D_2O, CH_3NO_2) δ 4.85 (s, 2 H), 3.30–4.10 (m, 3 H), 2.92 (s, $^+NCH_3$), 2.78 (s, NCH_3) and 2.60–3.02 (m) (8 H), 1.48 (s, 6 H).

The oxazolinium iodide (122 g, 0.361 mol) in 600 mL of anhydrous methanol was cooled to 0 °C. A solution of $NaBH_4$ (40 g, 1.05 mol) in 300 mL of dry methanol was added over a 1.0-h period. $NaBH_4$ (20 g, 0.526 mol) was then added at 0 °C in small portions, and stirring at 0 °C was continued for 2 h. Concentration of the reaction mixture afforded a gel which was dissolved in 300 mL of H_2O and extracted with four 250-mL portions of $CHCl_3$. The organic solution was dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a yellow oil (85 g). The oil was chromatographed on silica gel G. Elution with ether–hexane and methanol–ether solutions afforded 50.0 g (65%) of the pure oxazolidines **16**: NMR (CCl_4) δ 1.10 (s) and 1.0 (s) (6 H), 1.90–2.60 (m) and 2.12 (s) (6 H), 2.72 (s, 3 H), 2.85–3.70 (m, 4 H), 4.0 (m, 1 H); IR (neat) 1670 cm^{-1}. Anal. Calcd for $C_{11}H_{20}N_2O_2$: C, 62.24; H, 9.50; N, 13.20. Found: C, 61.76; H, 9.84; N, 12.92.

3-Formyl-1-methyl-5-oxopyrrolidine (17). The oxazolidines (26 g, 0.123 mol) were divided into five 4.0-g (0.0189 mol) portions and one 6.0-g (0.0283 mol) portion. The five 4.0-g portions of the oxazolidines were dissolved in an aqueous CF_3CO_2H–THF solution [CF_3CO_2H (5.4 g, 0.0474 mol), THF (5 mL), and H_2O (3 mL)]. The 6.0-g oxazolidine portion was dissolved in an aqueous CF_3CO_2H–THF solution [CF_3CO_2H (7.7 g, 0.0675 mol), THF (7 mL), and H_2O (4 mL)]. The reaction mixtures were stirred at room temperature for 6 h, combined, diluted with 2 L of $CHCl_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was chromatographed on silica gel G. Elution with ether–hexane solutions and ether removed the trifluoroacetic acid. The column was then stripped with MeOH–ether solutions. The organic solution was concentrated in vacuo and the residue was chromatographed on a prewashed (Et_2O) ion-exchange resin, Dowex 50-W. Elution with ether and $CHCl_3$ solutions afforded 15 g of crude **17** after drying and concentrating of the organic solvents in vacuo. The crude aldehyde (15 g) was then chromatographed on silica gel G. Elution with ether–hexane, ether, and metha-

nol–ether solutions gave 11.7 g (75%) of **17**. Distillation afforded 9.1 g (58%) of the pure aldehyde **17**: bp 100 °C (0.05 mm); NMR ($CDCl_3$) δ 2.30–2.95 (m) and 2.85 (s) (5 H), 2.95–3.90 (m, 3 H), 9.65 (s, 1 H); IR (neat) 1675 cm^{-1}. Anal. Calcd for $C_6H_9NO_2$: C, 56.88; H, 7.13; N, 11.01. Found: C, 56.30; H, 7.15; N, 11.31.

(*E*)-3-(3-Oxo-1-octenyl)-1-methyl-5-oxopyrrolidine (18). Dimethyl (2-oxoheptyl)phosphonate (20.2 g, 0.0910 mol) in 60 mL of THF was cooled to 0 °C under N_2. A hexane solution of 2.42 M *n*-BuLi (37.6 mL, 0.0910 mol) was added with a syringe, and the resulting reaction mixture was stirred at 0 °C for 30 min. The lactam aldehyde **17** (11.8 g, 0.0930 mol) in 50 mL of dry THF was added over a 5-min period, and stirring was continued at 0 °C for 4.5 h. The reaction mixture was diluted with 100 mL of ice–water and extracted with three 200-mL portions of CH_2Cl_2. The organic solution was dried over $MgSO_4$, filtered and concentrated in vacuo to afford 27 g of an oil. The oil was chromatographed on silica gel G. Elution with ether–hexane solutions and ether gave 14.2 g (70%) of the enone **18**: NMR (CCl_4) δ 0.90 (t) and 1.08–1.80 (m) (9 H), 1.85–3.71 (m) and 2.75 (s) (10 H), 6.01 (d, 1 H, $J_{13,14}$ = 15.0 Hz), 6.70 (dd, 1 H, $J_{12,13}$ = 7.5 Hz, $J_{13,14}$ = 15 Hz); IR (neat) 1600 (br), 1540 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.26; H, 9.33; N, 6.03.

(*E*)-3-(3-Hydroxy-1-octenyl)-1-methyl-5-oxopyrrolidines (19). The enone **18** (2.36 g, 0.0106 mol) in 30 mL of dry THF was cooled to −78 °C under N_2. A THF solution of 1.0 M lithium triethylborohydride (12.7 mL, 0.0127 mol) was added dropwise with a syringe, and stirring at −78 °C was continued for 15 min. The reaction mixture was then allowed to warm to room temperature, diluted with 100 mL of H_2O, and extracted with three 150-mL portions of ether. The organic extracts were washed with H_2O, dried, and concentrated in vacuo. Chromatography of the oil on silica gel and elution with ether–hexane and MeOH–ether solutions gave 1.8 g (75%) of the epimeric alcohols **19**: NMR ($CDCl_3$) δ 5.45–5.70 (m, 2 H), 4.0 (s, br, 1 H), 2.80 (s) and 1.80–3.80 (m) (9 H), 0.90 (t, distorted) and 1.05–1.75 (m) (11 H); IR (neat) 3425 (br), 1690 cm^{-1}; mass spectrum, *m/e* 225 (M), 208, 196, 154, 98. Anal. Calcd for $C_{13}H_{23}NO_2$: C, 69.30; H, 10.29; N, 6.22. Found: C, 69.40; H, 10.59; N, 6.15.

(*E*)-1-Methyl-5-oxo-3-[3-[(tetrahydro-2*H*-pyranyl-2-yl)-oxy]-1-octenyl]pyrrolidines (20). A solution of the lactam alcohols **19** (2.80 g, 0.0124 mol), dihydropyran (1.57 g, 0.0187 mol), and *p*-toluenesulfonic acid (60 mg) in 40 mL of CH_2Cl_2 was stirred at room temperature for 18 h. The reaction mixture was extracted with 10% $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated in vacuo. The oil was chromatographed on silica gel. Elution with ether–hexane solutions gave 2.7 g (71%) of the tetrahydropyranyl lactams **20**: NMR ($CDCl_3$) δ 0.90 (t, distorted) and 1.05–1.95 (m) (17 H), 2.10–4.20 (m) and 2.78 (s) (11 H), 4.32–4.67 (m, 1 H), 5.10–5.66 (m, 2 H); IR (neat) 1690 cm^{-1}. Anal. Calcd for $C_{18}H_{31}NO_3$: C, 69.86; H, 10.10; N, 4.53. Found: C, 69.62; H, 10.07; N, 4.43.

(*E*)-7-[3-(3-Hydroxy-1-octenyl)-1-methyl-5-oxo-4-pyrrolidinyl]-5-heptynoic Acids (21). A hexane solution of 2.3 M *n*-BuLi (2.78 mL, 0.00640 mol) was added with a syringe to diisopropylamine (0.808 g, 0.0080 mol) in 30 mL of THF at −78 °C, and stirring was continued for 10 min. The tetrahydropyranyl lactams **20** (2.0 g, 0.0065 mol) in 20 mL of THF were added dropwise and stirring was continued for 20 min at −78 °C. Methyl 7-bromo-5-heptynoate (0.70 g, 0.0320 mol) in 20 mL of THF was added, and stirring was continued at −78 °C for 2 h. The reaction was then allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with H_2O and extracted with ether. The organic solution was dried (Na_2SO_4), filtered, and concentrated in vacuo to afford an oil. The oil was passed through a short silica gel column, and the latter fractions resulting from elution with ether–hexane solutions, CH_2Cl_2, and MeOH–CH_2Cl_2 solutions were combined, dried (Na_2SO_4), and concentrated in vacuo to afford 2.5 g of an oil.

The oil (2.5 g) was dissolved in an aqueous methanolic sodium hydroxide solution [NaOH (0.72 g), H_2O (15 mL), and MeOH (45 mL)], and the reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The organic solution was washed with 2% NaOH, and the aqueous solutions were combined, cooled in an ice bath, acidified with HCl, and extracted with CH_2Cl_2. The organic solution was dried (Na_2SO_4), filtered, and concentrated in vacuo to afford approximately 1 g of the crude tetrahydropyranyl acids. The crude acids were dissolved in an aqueous acetic acid–THF solution [AcOH (45 mL), THF (15 mL), and H_2O (15 mL)] and stirred overnight at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo to afford an oil. The oil was chromatographed on silica gel G. Elution with ether and methanol–ether solutions gave 700 mg (32%) of the alcohol acids **21**: NMR ($CDCl_3$) δ 0.90 (t, distorted) and 1.07–1.98 (m) (13 H), 2.03–4.25 (m) and 2.85 (s) (14 H), 5.40–5.80 (m, 2 H), 6.26 (s, br, 2 H, CO_2H, OH); IR (neat) 3400 (br), 1675, 1720 (sh) cm^{-1}. Anal. Calcd for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.95; H, 9.01; N, 3.88.

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