A Three-step Procedure for the Conversion of γ-Lactones into δ-Lactones

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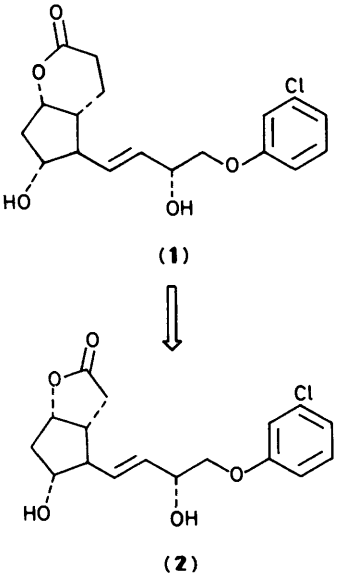
γ-Lactones with a wide range of functional groups are transformed by a three-step procedure into the corresponding δ-lactones in an overall yield of up to 55%. The novel methodology involves the reduction of a γ-lactone to a γ-lactol followed by a Horner olefination with an excess of lithiated diethyl α-cyano-α-dimethylaminomethylphosphonate to yield a mixture of *E*/*Z*-isomeric α-cyano enamines. Acidic hydrolysis of these intermediates affords the desired δ-lactones. By the same reaction sequence δ-lactones can be transformed into the corresponding ε-hydroxy carboxylic acids.

In connection with the synthesis of the main metabolite (**1**)[1] of the $PGF_{2\alpha}$ analogue cloprostenol we were interested in a mild and effective method for the ring enlargement of a γ-lactone to a δ-lactone.[2] The readily available intermediate (**2**)[3] was regarded as a suitable starting material (Scheme 1). However, the presence of unprotected hydroxy groups requires a reaction sequence not involving an oxidation step. According to our knowledge such a transformation has not yet been described in the literature.[4]

The synthetic problem of the required transformation is closely related to the one-carbon elongation of a carboxylic acid to the next higher homologue. Therefore, methods using the Horner, Wittig, or Peterson olefination of aldehydes to ketene *S*,*S*-acetals,[5] α-cyano enamines,[6] α-phosphono enamines,[7] α-cyano enol ethers,[8] or ketene *O*,*S*-acetals[9] seemed to be promising because these intermediates can be transformed by hydrolysis into the corresponding carboxylic acids. Indeed, these methods do not involve an oxidation step, but they require the reduction of the carboxylic acid to the corresponding aldehyde prior to the one-carbon elongation.

On the basis of these considerations we were able to transform the γ-lactone (**2**)[3] into the δ-lactone (**1**) using diethyl α-cyano-α-dimethylaminomethylphosphonate as the reagent for the chain elongation.[2] In this special case we did not succeed in the preparation of the corresponding ketene *S*,*S*-acetal[5] or α-phosphono enamine,[7] indicating the superiority of diethyl α-cyano-α-dimethylaminomethylphosphonate as a readily available and reactive olefination reagent.[6]

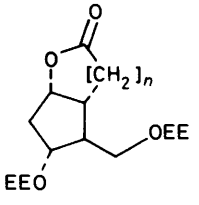


Scheme 1. Retrosynthesis of the cloprostenol metabolite (**1**)

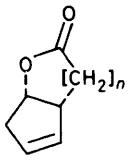
Results and Discussion

The conversion of the lactones (**3a**—**d**)[10–13] into the lactols (**5a**—**d**) was performed in almost quantitative yield by reduction with di-isobutylaluminium hydride (DIBAL) in toluene at −78 °C.[14] The diastereoselectivity of this reaction was not investigated because the chirality of the newly formed asymmetric centre disappears in the next reaction step.

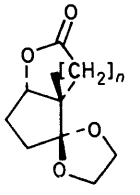
The olefination of the lactols (**5a**—**d**), using two equivalents of the lithiated diethyl α-cyano-α-dimethylaminomethyl-



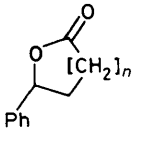
(**3a**)



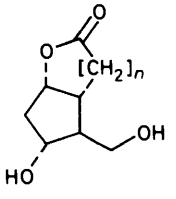
(**3b**)
(**4b**)



(**3c**)
(**4c**)



(**3d**)
(**4d**)

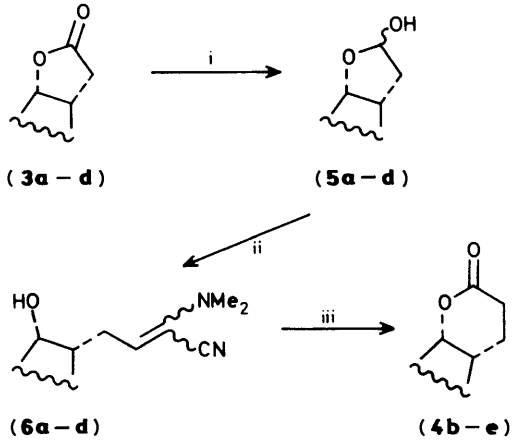


(**4e**)

n
(**3**) 1
(**4**) 2

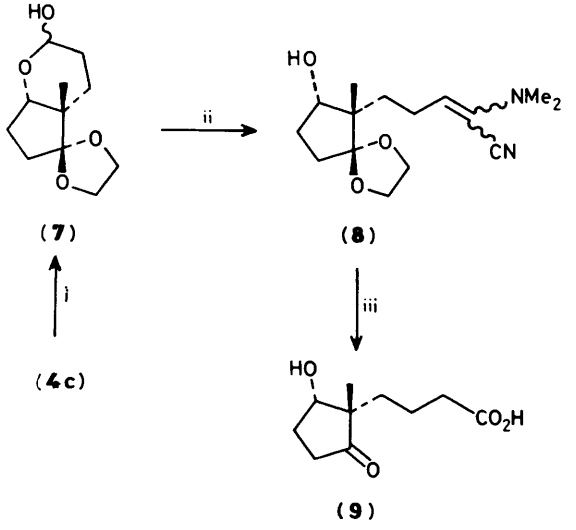
EE = CH(OEt)Me

phosphonate in tetrahydrofuran (THF) at 65 °C, afforded a mixture of the *E*- and *Z*-isomers of the α-cyano enamines (**6a**—**d**) (Scheme 2). Owing to the disappearance of the double bond in the next reaction step, it was not necessary to separate the geometric isomers. Therefore, the crude cyano enamines (**6a**—**d**) were hydrolysed in a mixture of acetic acid, THF, and water (2:2:1) at 60 °C, yielding the δ-lactones (**4b**—**e**), which were purified by column chromatography. The α-ethoxyethyl protecting groups of compound (**3a**) were removed during the hydrolysis, but the acetal group of compound (**3c**) proved to be stable under the reaction conditions. In most cases the overall yield of this three-step procedure ranged between 40 and 55%. Depending on the reaction conditions the γ-lactones may be variously substituted. Their additional functional groups, however, have to tolerate DIBAL reduction and acidic hydrolysis.



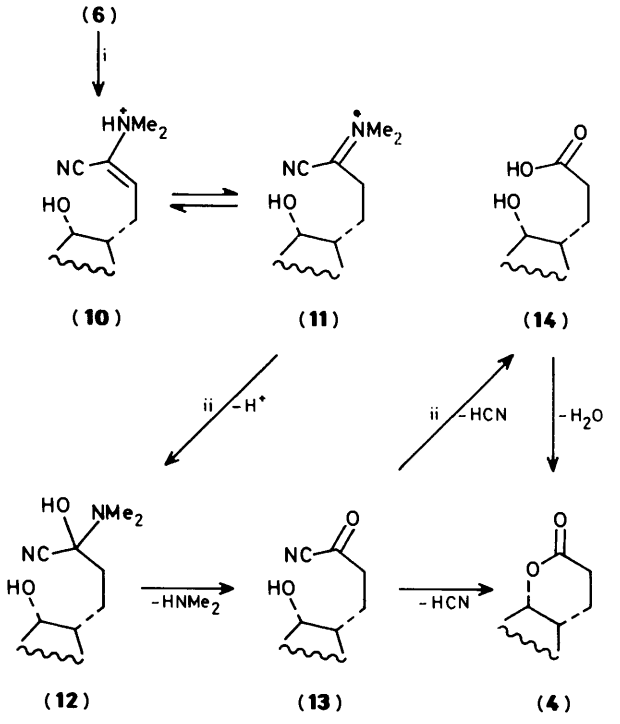
Scheme 2. Three-step procedure for the conversion of the γ-lactones (**3a**—**d**) into the δ-lactones (**4b**—**e**). *Reagents and conditions:* i, DIBAL, toluene, −78 °C; ii, $(EtO)_2P(O)CH(CN)NMe_2$, Bu^nLi, THF, 65 °C, 2 h; iii, AcOH–THF–water (2:2:1), 65 °C, 2 h

When the δ-lactone (**4c**) was subjected to the described reaction sequence the ε-hydroxy carboxylic acid (**9**) was obtained in an overall yield of 42% (Scheme 3). However, owing to the diminished ring-closure tendency of ε-hydroxy carboxylic acids a seven-membered ε-lactone is not formed.



Scheme 3. Conversion of the δ-lactone (**4c**) into the ε-hydroxy carboxylic acid (**9**). *Reagents and conditions:* i, DIBAL, toluene, −78 °C; ii, $(EtO)_2P(O)CH(CN)NMe_2$, Bu^nLi, THF, 65 °C, 2 h; iii, AcOH–THF–water (2:2:1), 65 °C, 2 h

The mechanism of the transformation of the α-cyano enamines (**6**) into the δ-lactones (**4**) may be explained in accordance with earlier observations concerning the acidic hydrolysis of α-phosphono enamines [7] as shown in Scheme 4.



Scheme 4. Mechanistic consideration of the conversion of the α-cyano enamines (**6**) into the δ-lactones (**4**). *Reagents:* i, H^+; ii, water

The protonation of the enamine (**6**) affords the enaminium salt (**10**) which is in equilibrium with the iminium salt (**11**). Addition of water and elimination of dimethylamine yields the acyl cyanide (**13**) *via* the intermediate (**12**). Acyl cyanides are known to be mild acylation reagents.[15] Therefore, they may be directly cyclized to the δ-lactone (**4**) or, alternatively, first hydrolysed to the δ-hydroxy acid (**14**), which then cyclizes spontaneously to the δ-lactone (**4**) in the acidic medium.

Experimental

^1H N.m.r. spectra were recorded at 100 MHz on a Tesla BS 567 instrument. ^{13}C N.m.r. spectra were measured at 20 MHz on a Varian CFT 20 spectrometer. Chemical shifts are reported in δ values related to tetramethylsilane. Low-resolution electron impact (e.i.) and chemical ionization (c.i.) mass spectra were obtained on a GC/MS-Datensystem HP 5985 B spectrometer. High-resolution mass spectra were recorded on a Finnigan-MAT 212 spectrometer. I.r. spectra were measured on a Specord 75 IR spectrometer (Carl Zeiss Jena). Flash chromatography [16] was performed on silica gel 60 (0.063—0.04 mm).

Reduction of the Lactones (**3a**—**d**) *and* (**4c**) *to the Lactols* (**5a**—**d**) *and* (**7**).—*General procedure.* DIBAL (2.14 g, 15 mmol) was dissolved in toluene (15 ml) and the solution was added dropwise within 5 min to a solution of one of the lactones (**3a**—**d**) or (**4c**) (10 mmol) in toluene (15 ml) at −78 °C under argon. After 30 min methanol (2 ml) was added. The solution was allowed to warm up to room temperature, mixed with brine (50 ml), and was filtered through a layer of sand. The sand was washed with ethyl acetate (3 × 20 ml). The combined filtrates and washings were extracted with ethyl acetate (3 × 20 ml). The

extract was dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford the corresponding lactol (**5a**—**d**) or (**7**) in almost quantitative yield. These products were used in the next step without further purification.

Olefination of the Lactols (**5a**—**d**) *and* (**7**) *to the α-Cyano Enamines* (**6a**—**d**) *and* (**8**).—*General procedure.* A hexane solution (18.3 ml) of butyl-lithium (1.2M; 22 mmol) was added under argon at room temperature to a stirred solution of diethyl α-cyano-α-dimethylaminomethylphosphonate (4.85 g, 22 mmol) in THF (20 ml). Thereafter a solution of a lactol (**5a**—**d**) or (**7**) (10 mmol) in THF (10 ml) was added and the mixture was boiled under reflux for 2 h, then cooled to room temperature, and saturated aqueous ammonium chloride (20 ml) was added. The mixture was extracted with diethyl ether (3 × 50 ml). The extract was dried (Na_2SO_4), and concentrated under reduced pressure. The residue, a mixture of the crude α-cyano enamines (**6a**—**d**) and (**8**) and phosphorus-containing by-products, was used for the next process without further purification.

Hydrolysis of the α-Cyano Enamines (**6a**—**d**) *and* (**8**) *to the δ-Lactones* (**4b**—**e**) *and the ε-Hydroxy Acid* (**9**), *respectively.*—*General procedure.* A crude α-cyano enamine (**6a**—**d**) or (**8**) obtained according to the foregoing procedure was dissolved in a mixture of acetic acid (20 ml), THF (20 ml), and water (10 ml). The mixture was heated for 2 h at 60 °C and then concentrated under reduced pressure to afford a crude product, from which the corresponding δ-lactone (**4b**—**e**) or the ε-hydroxy acid (**9**) was isolated according to the individual procedures given below.

(1SR,6RS)-2-*Oxabicyclo*[4.3.0]*non*-7-*en*-3-*one* (**4b**). The crude product was purified by flash chromatography with dichloromethane–ethyl acetate (20:1) as eluant and was then subjected to Kugelrohr distillation (bath temperature 175 °C; 50 Pa) to afford the δ-*lactone* (**4b**) [280 mg, 20% based on (**3b**)] as a liquid (Found: C, 69.9; H, 7.5. $C_8H_{10}O_2$ requires C, 69.5; H, 7.3%); $\nu_{max.}$(liquid film) 3 050 (=CH), 1 725 (C=O), and 1 240 cm^{-1} (C–O–C); δ_H 1.60—3.05 (6 H, superimposed signals, 4-, 5-, and 9-H_2), 3.12 (1 H, m, 6-H), 5.08 (1 H, dt, *J* 3 and 5 Hz, 1-H), and 5.58 and 5.81 (2 H, 2 m, HC=CH); δ_C 22.70 (t, C-5), 28.35 (t, C-4), 41.34 (t, C-9), 42.51 (d, C-6), 80.79 (d, C-1), 129.73 and 131.56 (2 d, CH=CH), and 172.32 (s, C-3); *m/z* (e.i.) 138 (M^+, 15%). 20 ($M^+ - H_2O$, 22), 109 (22), 96 ($M^+ - CO_2$, 28), 95 (19), 81 (39), 79 (35), and 67 (100).

(1SR,6SR)-7,7-*Ethylenedioxy*-6-*methyl*-2-*oxabicyclo*[4.3.0]-*nonan*-3-*one* (**4c**). The crude product was purified by flash chromatography on silica gel 60 with dichloromethane–ethyl acetate (20:1) to yield the lactone (**4c**) [1.077 g, 51% based on (**3c**)] as crystals, m.p. 65—66 °C (from diethyl ether–n-hexane) (Found: C, 62.1; H, 7.6. $C_{11}H_{16}O_4$ requires C, 62.25; H, 7.6%); $\nu_{max.}$(KBr) 1 725 (C=O) and 1 250 cm^{-1} (C–O–C); $\delta_H(CDCl_3)$ 1.13 (3 H, s, 6-Me), 3.92 (4 H, t, *J* 4 Hz, O[CH_2]$_2$O), and 4.36 (1 H, m, 9-H); $\delta_C(CDCl_3)$ 21.03 (q, 6-Me), 25.70 (t, CH_2), 27.91 (2 t, 2 × CH_2), 32.27 (t, CH_2), 44.65 (s, C-6), 64.73 and 65.03 (2 t, O[CH_2]$_2$O), 86.34 (d, C-1), 117.40 (s, C-7), and 172.91 (s, C-3); *m/z* (e.i.) 212 (M^+, 0.5%), 168 ($M^+ - CO_2$, 3.5), 153 (168 − CH_3, 2), 139 (10), 99 (12), and 86 (100).

(RS)-5-*Phenylpentan*-5-*olide* (**4d**). The crude product was dissolved in benzene (20 ml), mixed with toluene-*p*-sulphonic acid (10 mg), and the solution was refluxed for 2 h, washed with saturated aqueous sodium hydrogen carbonate (5 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was filtered through silica gel 60 (50 g; 0.2—0.5 mm) with dichloromethane and then purified by flash chromatography with dichloromethane to afford the δ-lactone (**4d**) [516 mg, 53% based on (**3d**)] as crystals, m.p. 72—73 °C (from diethyl ether) (lit.,[17] 74—76 °C) (Found: C, 75.1; H, 6.8. Calc. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.9%); $\nu_{max.}$(KBr) 1 725 (C=O), 1 250 (C–O–C), and 710 and 765 cm^{-1} (C_6H_5); $\delta_H(CDCl_3)$ 2.63 (2 H, m, 2-H_2), 5.35 (1 H, m, 5-H), and 7.74 (5 H, s, Ph); $\delta_C(CDCl_3)$ 18.52, 29.45, and 30.42 (3 t, 3 × CH_2), 81.51 (d, C-5), 125.69, 128.18, and 128.53 (3 d, aromatic CH), 139.91 (s, aromatic C), and 171.23 (s, C=O); *m/z* (e.i.) 176 (M^+, 63%), 148 ($M^+ - CO$, 3.5), 132 ($M^+ - CO_2$, 10), 120 (13), 107 (11), 106 (16), 104 ($C_6H_5CH{=}CH_2^+$, 100), 78 (14), 77 ($C_6H_5^+$, 27), and 70 (94).

(1SR,6RS,7SR,8RS)-8-*Hydroxy*-7-*hydroxymethyl*-2-*oxa-bicyclo*[4.3.0]*nonan*-3-*one* (**4e**). To remove the bulk of the organophosphorus compounds the crude product was deposited on silica gel 60 (0.2—0.5 mm; 50 g) and eluted first with dichloromethane–ethyl acetate (5:1; 700 ml) and then with ethyl acetate–methanol (9:1; 500 ml). The product from the second elution was purified by flash chromatography on silica gel 60 with ethyl acetate–methanol (85:15) to afford the δ-*lactone* (**4e**) [767 mg, 41% based on (**3a**)] as an oil (Found: C, 54.8; H, 7.8. $C_9H_{14}O_4{\cdot}CH_3OH$ requires C, 55.05; H, 8.3%); $\nu_{max.}$(liquid film) 3 360 (OH), 2 480 (OH), 1 720 (CO), and 1 250 cm^{-1} (C–O–C); $\delta_H(CD_3OD)$ 3.67 (2 H, d, *J* 4 Hz, 7-CH_2OH), 3.99 (1 H, q, *J* 7.5 Hz, 8-H), and 4.77 (1 H, m, 9-H); $\delta_C([^2H_6]$acetone) 23.53 (t, C-5), 29.17 (t, C-4), 37.90 (t, C-9), 42.02 (d, C-7), 54.83 (d, C-6), 62.02 (t, 7-CH_2OH), 72.76 (d, C-8), 80.87 (d, C-1), and 171.53 (s, C-3).

The dibenzoate of (**4e**) was an oil (Found: $M^+ - C_6H_5CO_2H$, 272.1053. $C_{16}H_{10}O_4$ requires *m/z*, 272.1049); *m/z* (e.i.) 272 ($M^+ - C_6H_5CO_2H$, 3.5%), 150 ($M^+ - 2C_6H_5CO_2H$, 19), 105 (100), and 77 (20).

The *bis-dimethyl-t-butylsilyl ether* of (**4e**) was obtained as crystals, m.p. 62—65 °C (from ethanol–water) (Found: C, 61.1; H, 10.2. $C_{21}H_{42}O_4Si_2$ requires C, 60.8; H, 10.2%); *m/z* (c.i.) 415 ($M^+ + 1$, 100%), 399 ($M^+ - CH_3$, 15), 357 (M^+ − t-C_4H_9, 10), 283 (32), 225 (10), 179 (22), 151 (77), and 133 (10).

4-[(1SR,2SR)-2-*Hydroxy*-1-*methyl*-5-*oxocyclopentyl*]-*butanoic acid* (**9**). A solution of the crude product in dichloromethane (50 ml) was extracted with saturated aqueous sodium hydrogen carbonate. The extract was adjusted with 1M aqueous hydrogen chloride to pH 1 and extracted continuously for 6 h with diethyl ether. After evaporation of the ether the residue was purified by flash chromatography on silica gel with dichloromethane–acetonitrile–acetic acid (4:2:0.1) to afford the ε-*hydroxy acid* (**9**) [682 mg, 42% based on (**4c**)] as crystals, m.p. 97—99 °C (from diethyl ether–n-hexane) (Found: C, 59.1; H, 8.0. $C_{10}H_{16}O_4{\cdot}0.25H_2O$ requires C, 58.9; H, 8.0%); $\nu_{max.}$(KBr) 3 460 and 3 035 (OH) and 1 710 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 0.87 (3 H, s, 1-Me), 4.10 (1 H, t, *J* 3 Hz, 2-H), and 6.10 (2 H, br s, OH and CO_2H, exchangeable with D_2O).

Methyl Ester of Acid (**9**).—This *methyl ester* was prepared by treatment of the acid (**9**) with a solution of diazomethane in diethyl ether, and was obtained as a liquid (Found: M^+, 214.1213, $C_{11}H_{18}O_4$ requires *M*, 214.1205); $\nu_{max.}$(liquid film) 3 450 (OH) and 1 725 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 0.86 (3 H, s, 1-Me), 3.03 (1 H, br s, OH, exchangeable with D_2O), 3.56 (3 H, s, CO_2Me), and 4.08 (1 H, t, *J* 4 Hz, 2-H); δ_C ($CDCl_3$) 18.89 (q and t, CH_2 and CH_3), 27.38, 29.33, 33.41, and 33.98 (4 t, 4 × CH_2), 51.80 (q, OMe), 53.69 (s, C-1), 76.88 (d, C-2), 174.96 (s, CO_2Me), and 221.15 (s, C-5); *m/z* (e.i.) 214 (M^+, 40%), 196 ($M^+ - H_2O$, 70), 127 (70), 98 (100), 81 (60), and 55 (22).

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