A New Synthesis of α-Methylene Lactones

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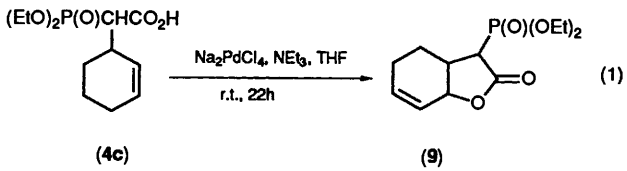
Various α-diethoxyphosphoryl-γ, δ-unsaturated acids were synthesized in good yields *via* alkylation of ethyl (diethoxyphosphoryl)acetate with allylic bromides. Iodo- and seleno-lactonization led to α-phosphono-iodo and -seleno lactones, which underwent Wittig–Horner reaction with paraformaldehyde to produce α-methylene-γ-lactones in very good yields. This methodology was applied to a short synthesis of frullanolide.

The development of versatile synthetic methods for α-methylene lactones has been thoroughly studied, but is still a subject of continuing interest, since many naturally occurring compounds having the α-methylene-γ-butyrolactone ring exhibit useful biological properties.[1] A recent review has classified the large number of reported synthetic methods for α-methylene lactones, and has pointed out that the synthesis of α-methylene lactones *via* the Wittig reaction has been limited to a few specific cases.[1b] We now report a convenient synthesis of α-phosphorylated γ-lactones and their successful utilization as Wittig–Horner reagents for the synthesis of α-methylene-γ-lactones.[2] We also describe the application of this methodology to the synthesis of the natural product frullanolide.

Results and Discussion

Synthesis of α-Diethoxyphosphoryl-γ-butyrolactones and α-Methylene-γ-butyrolactones.—Treatment of ethyl (diethoxyphosphoryl)acetate carbanion (**1**) with allylic bromides such as compounds (**2a–d**) under mild conditions (0 °C to room temperature) led to the expected α-monoallylated phosphonoacetates (**3a–d**) in good yield (Table 1). Hydrolysis of the phosphonoacetates (**3a–d**) in aqueous ethanol containing K_2CO_3 gave the corresponding α-diethoxyphosphoryl-γ,δ-unsaturated acids (**4a–d**) in quantitative yields. Iodolactonization[3a] of the acids (**4a–d**) led to the desired α-diethoxyphosphoryl-γ-lactones (**5a–d**) in 61–88% yield. Treatment of the acids (**4a–d**) with benzeneselenenyl bromide under mild conditions produced the corresponding phenylselenolactonization products (**6a–d**)[3b,c] in 57–83% yield (Scheme 1).

Treatment of the iodo lactones (**5b** and **c**) with diazabicycloundecene (DBU)[4] in benzene at reflux smoothly led to dehydroiodination products (**7**) and (**9**) in good yield. Compound (**9**) was also obtained in 58% yield by oxidation of the selenide (**6c**) with H_2O_2, while similar treatment of the selenide (**6b**) led to α-diethoxyphosphoryl-γ-isopropenyl-γ-lactone (**8**) 83% yield). The lactone (**9**) was also conveniently synthesized *via* palladium(II)-catalysed cyclization of compound (**4c**) (44% yield) [equation (1)].[5]



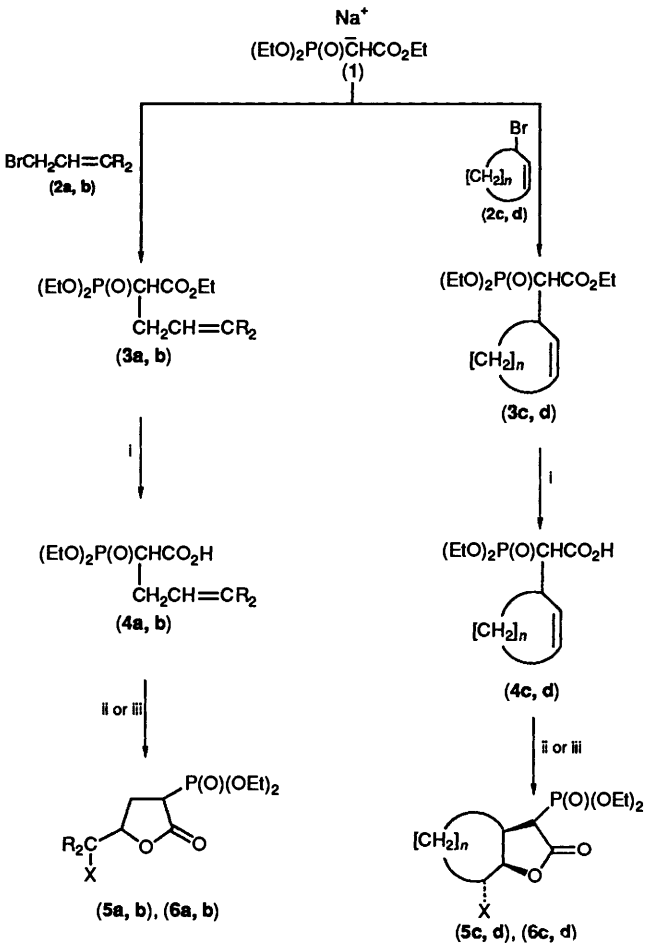
(4c) (9) (1)

Hydrogenation of compound (**9**) over a palladium catalyst led to the lactone (**10**) in 94% yield, alternatively prepared in good yield by reduction of the iodo lactone (**5c**) or the seleno

Table 1. Alkylation of carbanion (**1**) with allylic bromides.

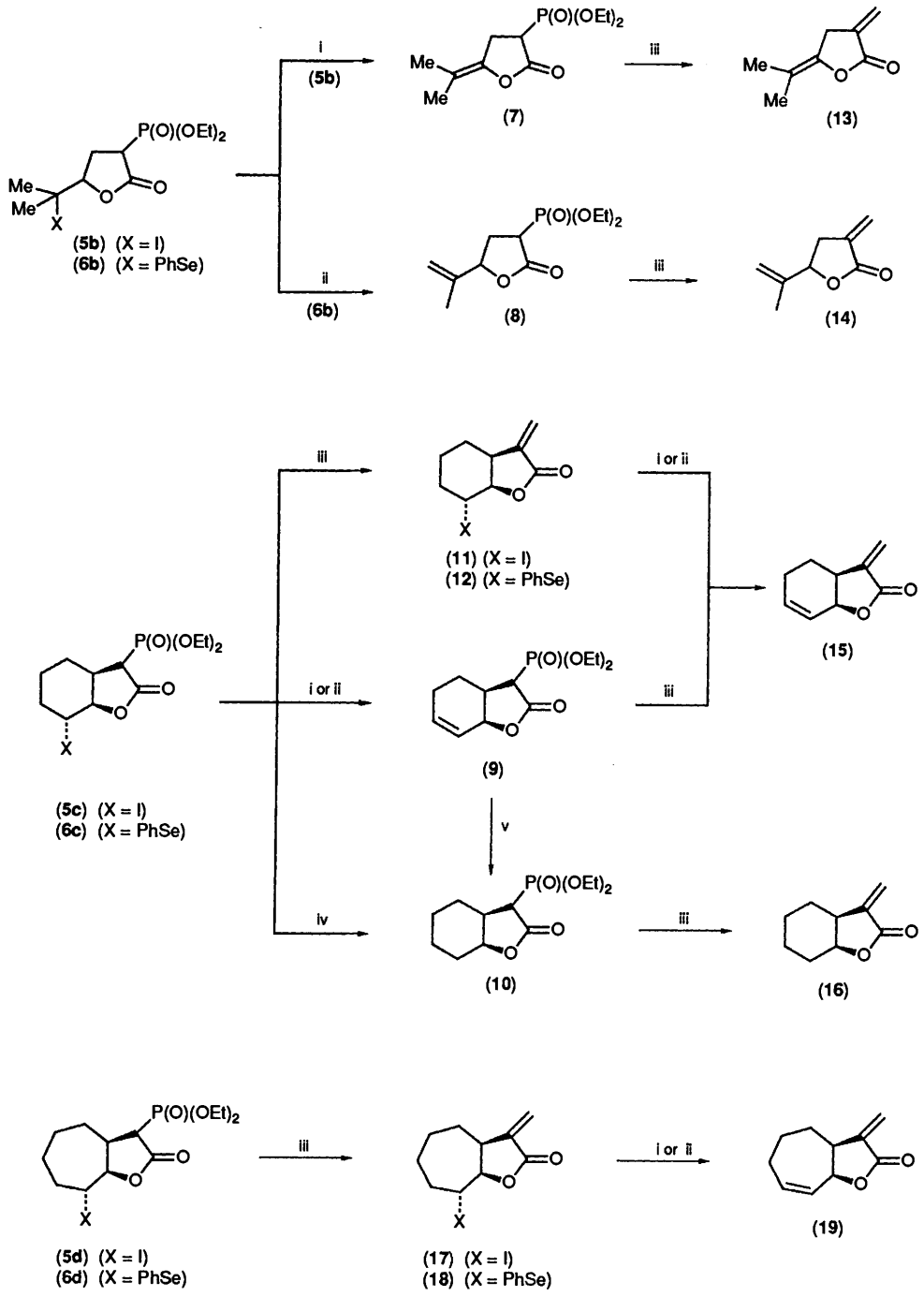
Entry	Allylic bromide	Adduct	Yield (%)[a]
1	(**2a**) (R = H)	(**3a**)	90
2	(**2b**) (R = Me)	(**3b**)	92
3	(**2c**) (*n* = 3)	(**3c**)	79
4	(**2d**) (*n* = 4)	(**3d**)	72
5	(**20**)	(**21**)	85

[a] Isolated yield.



a; R = H, **b**; R = Me, **c**; *n* = 3, **d**; *n* = 4, (**5**); X = I, (**6**); X = PhSe

Scheme 1. *Reagents:* i, OH^-; ii, $NaHCO_3$, I_2, KI_{aq}; iii, PhSeBr, THF.



Scheme 2. *Reagents:* i, DBU, benzene; ii, H_2O_2 or MCPBA, CH_2Cl_2; iii, NaH, $(HCHO)_n$, THF; iv, Bu_3SnH, AIBN, benzene; v, Pd/C, H_2.

lactone (**6c**) with tributyltin hydride in the presence of azoisobutyronitrile (AIBN). The α-phosphoryl-γ-lactones thus obtained were treated with sodium hydride to generate α-phosphoryl-γ-lactone carbanions; following Wittig–Horner reaction with paraformaldehyde the desired α-methylene-γ-lactones * (**11**)–(**18**) were obtained in good yield (Table 2, Scheme 2).

Treatment of the α-methylene iodo lactones (**11**) and (**17**) with DBU or the corresponding seleno derivatives (**12**) and (**18**) with H_2O_2 similarly led to the expected α-methylene lactones (**15**) and (**19**), respectively, in good to moderate yield (entries 5, 6, 11, and 12 in Table 2).

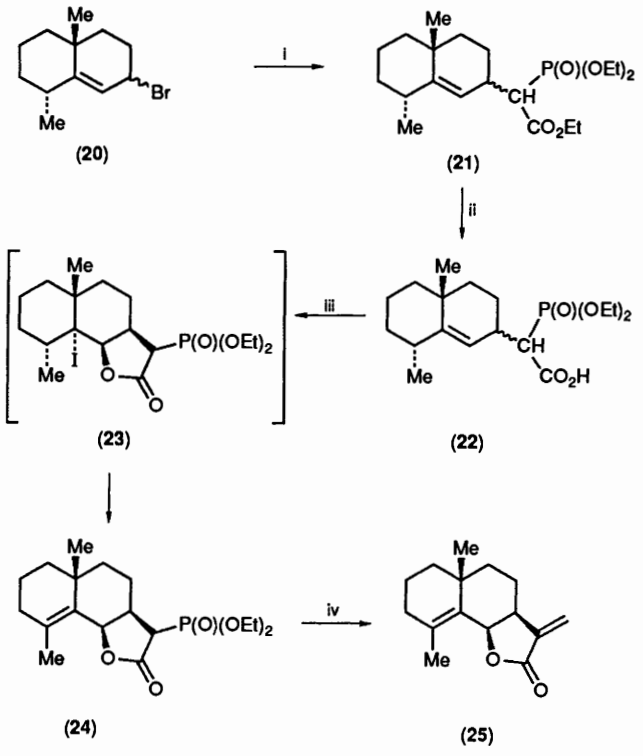
Synthesis of Frullanolide.—As mentioned above, the Wittig–Horner reaction is very useful for the synthesis of α-methylene-γ-lactones due to its generality and simplicity. We therefore sought to apply this methodology to the synthesis of the natural product frullanolide (**25**), which is an allergenically active α-methylene-γ-butyrolactone sesquiterpene.[7] Following the procedure described above, treatment of the carbanion (**1**) with 7-bromo-1,4a-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene

* The ^1H NMR spectral data of the *cis*-fused α-methylene-γ-lactones (**15**) and (**16**) are identical with those of samples prepared by different methods.[6]

Table 2. Synthesis of α-methylene-γ-lactones[a] (**11**)–(**19**).

Entry	Starting material	Product	Yield (%)[b]
1	(**7**)	(**13**)	63
2	(**8**)	(**14**)	43
3	(**5c**)	(**11**)	91
4	(**6c**)	(**12**)	100
5[c]	(**11**)	(**15**)	85
6[d]	(**12**)	(**15**)	59
7	(**9**)	(**15**)	87
8	(**10**)	(**16**)	75
9	(**5d**)	(**17**)	59
10	(**6d**)	(**18**)	80
11[c]	(**17**)	(**19**)	45
12[d]	(**18**)	(**19**)	80

[a] *via* Wittig–Horner reaction of α-phosphoryl-γ-lactones with paraformaldehyde, unless otherwise indicated. [b] Isolated yield. [c] *via* Dehydroiodination of the iodo lactone (**11**) or (**17**). [d] *via* Oxidation of the seleno lactone (**12**) or (**18**).



Scheme 3. *Reagents:* i, NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF; ii, NaOH, aq. EtOH; iii, $NaHCO_3$, I_2, KI, aq. THF; iv, NaH, $(HCHO)_n$, THF.

(**20**)* led to a mixture of two stereoisomeric ethyl 2-diethoxyphosphoryl-2-(4a,8-dimethyl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2-yl)acetate (**21**) (85% yield). The mixture was hydrolysed to give the corresponding α-(4a,8-dimethyl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2-yl)acetic acid (**22**) as a *ca.* 5:3 mixture of the pseudoequatorial acid and its axial isomer, for which the ratio was determined by comparison of the intensity of the phosphonate α-carbon resonances in the ^{13}C NMR spectrum of the mixture.† The acid (**22**) similarly underwent iodolactonization to give α-phosphoryl-γ-lactone (**24**) (47%), which was produced *via* dehydroiodination of an initially formed iodo lactone (**23**) under the reaction conditions employed, and recovered acid (**22**) was enriched with one of the two isomers having an axial C-2 substituent.‡ The Wittig–Horner reaction of α-phosphoryl lactone (**24**) with paraformaldehyde gave frullanolide (**25**)[8] in quantitative yield (Scheme 3).

Structural assignment for compound (**25**) was based on its IR and ^1H NMR spectral data, which were identical with those of a sample reported by Perold and co-workers.[7]

In conclusion, the following points from this investigation are pertinent: (1) a versatile synthetic method for α-phosphoryl-γ-lactones was established; (2) the α-phosphoryl lactones provided efficient synthons for α-methylene lactones.

Experimental

General.—^1H and ^{13}C NMR spectra were obtained on a JEOL JNM-FX-60 spectrometer for solutions in $CDCl_3$, operating at 60 and 15.04 MHz, respectively, with Me_4Si as internal standard. IR spectra were recorded with a Shimadzu IR-408 instrument. Mass spectra were taken with a JEOL DX-300 spectrometer.

Reaction of Triethyl Phosphonoacetate Carbanion (**1**) *with Allylic Bromides* (**2a–d**). *General Procedure.*—To a solution of anion (**1**), generated *in situ* from triethyl phosphonoacetate (ethyl diethoxyphosphonylacetate) (2.24 g, 10 mmol) and NaH (11 mmol) in dry tetrahydrofuran (THF) (25 ml) at 0 °C during 0.5 h, was added a bromide (**2**) (10 mmol). The mixture was allowed to warm to room temperature during 2 h, and it was then stirred at this temperature for 2 h. After being quenched with aq. NH_4Cl, the mixture was extracted with diethyl ether, washed with water, and dried over Na_2SO_4. Evaporation of the solvent, followed by chromatography (silica gel; $CHCl_3$), gave samples of γ,δ-unsaturated esters (**3a–d**). The yields of (**3a–d**) are summarized in Table 1. The products (**3a–d**) had the following properties.

Ethyl 2-(*diethoxyphosphoryl*)*pent-4-enoate* (**3a**). Oil; ν_{max}(neat) 1 730 and 1 635 cm^{-1}; δ_H 1.29 (3 H, t, *J* 7.1 Hz, Me), 1.34 (6 H, t, *J* 7.0 Hz, Me), 2.12–2.96 (3 H, m, $CHCH_2$), 3.72–4.60 (6 H, m, OCH_2), and 4.80–6.28 (3 H, m, $CH{=}CH_2$).

Ethyl 2-(*diethoxyphosphoryl*)-5-*methylhex*-4-*enoate* (**3b**). Oil; ν_{max}(neat) 1 730 and 1 630 cm^{-1}; δ_H 1.27 (3 H, t, *J* 7.2 Hz, Me), 1.34 (6 H, t, *J* 7.2 Hz, Me), 1.65 (6 H, s, Me), 2.66–3.25 (3 H, m, $CHCH_2$), 3.80–4.48 (6 H, m, OCH_2), and 4.94–5.16 (1 H, m, olefinic H).

Ethyl 2-(*diethoxyphosphoryl*)-2-(*cyclohex*-2′-*enyl*)*acetate* (**3c**). Oil; ν_{max}(neat) 1 730 and 1 640 cm^{-1}; δ_H 1.29 (3 H, t, *J* 7.1 Hz, Me), 1.33 (6 H, t, *J* 7.0 Hz, Me), 1.52–2.28 (6 H, br, CH_2), 2.56–3.20 (2 H, m, CH–CH), 3.62–4.56 (6 H, m, OCH_2), and 5.20–6.24 (2 H, m, olefinic H).

Ethyl 2-(*diethoxyphosphoryl*)-2-(*cyclohept*-2′-*enyl*)*acetate* (**3d**). Oil; ν_{max}(neat) 1 730 and 1 640 cm^{-1}; δ_H 1.29 (3 H, t, *J* 7.1 Hz, Me), 1.34 (6 H, t, *J* 7.0 Hz, Me), 1.48–2.48 (8 H, m, CH_2), 2.48–3.24 (2 H, m, CH–CH), 3.80–4.60 (6 H, m, OCH_2), and 5.44–6.00 (2 H, m, olefinic H).

Hydrolysis of Esters (**3a–d**).—A solution of an ester (**3**) (10

* The bromide (**20**) was prepared by treatment of a mixture of equatorial and axial 4a,8-dimethyl-2,3,4,4a,5,6,7,8-octahydronaphthalen-2-ol with phosphorus tribromide in dry benzene according to the reported procedures.[8e] The bromide (**20**) was used without separation of its individual isomers.

† The ^{13}C NMR spectrum ($CDCl_3$) of the acid (**22**) showed two doublets at δ_C 52.0 (J_{CP} 132.4 Hz) and δ_C 51.5 (J_{CP} 131.5 Hz) assignable to the phosphonate α-carbons of the equatorial and axial isomers, respectively.

‡ The ^{13}C NMR spectrum of the recovered acid (**22**) showed it to be a *ca.* 1:3.2 mixture of the equatorial and axial isomers.

mmol) in EtOH–water (1:1; 20 ml) containing K_2CO_3 (4.15 g, 30 mmol) was heated at reflux for 1 h. After evaporation of the solvent under reduced pressure, the residue was acidified with dil. HCl and extracted with $CHCl_3$, and the extract was washed with water and dried over Na_2SO_4. After removal of the solvent, crude 2-(diethoxyphosphoryl) carboxylic acids (**4a–d**) were used in the following lactonization reaction without purification.

Iodolactonization of Acids (**4a–d**).—To 0.2M aq. $NaHCO_3$ (30 ml) containing an acid (**4**) (5 mmol) was added an aqueous solution of KI (1.66 g, 10 mmol) and I_2 (1.40 g, 5.5 mmol) (10 ml). After the mixture had been stirred for 12 h at room temperature, saturated aq. Na_2SO_3 (30 ml) was added. The organic layer was extracted with $CHCl_3$, washed with water, and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel ($CHCl_3$) to give iodo lactones (**5a–d**) which had the following properties.

Compound (**5a**) (1.15 g, 64%); oil; ν_{max}(neat) 1 770 cm^{-1}; δ_H 1.37 (6 H, t, *J* 7.0 Hz, Me), 1.60–3.04 (3 H, m, lactone CH_2 and CH), 3.04–3.60 (2 H, m, CH_2I), and 3.84–4.92 (5 H, m, OCH_2Me and OCH).

Compound (**5b**) (1.71 g, 88%); oil; R_F 0.30 ($CHCl_3$); ν_{max}(neat) 1 770 cm^{-1}; δ_H 1.26 (6 H, t, *J* 7.1 Hz, Me), 1.71 (3 H, s, Me), 1.97 (3 H, s, Me), 2.12–3.20 (3 H, m, lactone CH_2 and CH), 3.84–4.40 (4 H, m, OCH_2Me), and 4.80–5.40 (1 H, br, OCH); *m/z* 390 (M^+).

Compound (**5c**) (1.23 g, 61%); oil; R_F 0.20 ($CHCl_3$); ν_{max}(neat) 1 770 cm^{-1}; δ_H 1.49 (6 H, t, *J* 7.0 Hz, Me), 1.52–2.20 (6 H, m, cyclohexane CH_2), 2.44–3.40 (2 H, m, lactone CH), 3.80–4.72 (5 H, m, OCH_2Me and CHI), and 5.00 (1 H, t, *J* 4.5 Hz, OCH); *m/z* 402 (M^+).

Compound (**5d**) (1.42 g, 68%); oil; ν_{max}(neat) 1 770 cm^{-1}; δ_H 1.38 (6 H, t, *J* 7.0 Hz, Me), 1.52–2.48 (8 H, br, cycloheptane CH_2), 2.48–3.12 (2 H, m, lactone CH), 3.80–4.68 (5 H, m, OCH_2Me and CHI), and 5.05 (1 H, dd, *J* 6.9 and 8.8 Hz, OCH).

Selenolactonization of Acids (**4a–d**).—A solution of benzeneselenenyl bromide (5 mmol) in dry THF (25 ml) was added to a stirred solution of an acid (**4**) (5 mmol) in dry THF (25 ml) at −78 °C. The reaction mixture was allowed to warm to room temperature during 2 h, and was then stirred at this temperature for 2 h. After saturated aq. $NaHCO_3$ had been added, the reaction was extracted with $CHCl_3$, and the extract was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed by preparative TLC (PLC) (silica gel; $CHCl_3$) to give seleno lactones (**6a–d**) as follows.

Compound (**6a**) (1.39 g, 71%); oil; ν_{max}(neat) 1 770 cm^{-1}; δ_H 1.30 (6 H, t, *J* 7.0 Hz, Me), 1.72–3.60 [5 H, m, $CH_2CHP(O)$ and CH_2SePh], 3.76–5.16 (5 H, m, OCH_2Me and OCH), and 7.00–7.80 (5 H, m, Ph).

Compound (**6b**) (1.20 g, 57%); oil; R_F 0.23 ($CHCl_3$); ν_{max}(neat) 1 770 cm^{-1}; δ_H 1.25–1.48 (12 H, m, Me), 2.39–2.96 [3 H, br, $CH_2CHP(O)$], 3.97–5.08 (5 H, m, OCH_2Me and OCH), and 7.27–7.73 (5 H, m, Ph).

Compound (**6c**) (1.79 g, 83%); oil; R_F 0.40 ($CHCl_3$); ν_{max}(neat) 1 770 cm^{-1}; δ_H 1.35 (6 H, t, *J* 6.9 Hz, Me), 1.52–2.40 (6 H, m, CH_2), 2.52–3.40 (2 H, m, lactone CH), 3.40–3.80 (1 H, m, $CHSePh$), 3.80–4.52 (4 H, m, OCH_2Me), 4.78 (1 H, t, *J* 4.4 Hz, OCH), and 7.00–7.80 (5 H, m, Ph); *m/z* 432 (M^+).

Compound (**6d**) (1.40 g, 63%); oil; R_F 0.55 ($CHCl_3$–MeOH 9:1); ν_{max}(neat) 1 765 cm^{-1}; δ_H 1.36 (6 H, t, *J* 7.0 Hz, Me), 1.04–2.48 (8 H, m, CH_2), 2.48–3.24 (2 H, m, lactone CH), 3.24–3.72 (1 H, m, $CHSePh$), 3.80–4.48 (4 H, m, OCH_2Me), 4.87 (1 H, t, *J* 6.8 Hz, OCH), and 7.0–7.64 (5 H, m, Ph); *m/z* 445 (M^+).

Palladium(II)*-catalysed Cyclization of Acid* (**4c**).—To a solution of acid (**4c**) (0.50 g, 1.81 mmol) in dry THF (7 ml) were added triethylamine (0.37 g, 3.66 mmol) and Na_2PdCl_4 [9] (0.53 g, 1.81 mmol). The mixture was stirred at room temperature for 22 h. After the resulting insoluble salt had been removed by filtration, the filtrate was quenched with water. The organic layer was extracted with $CHCl_3$, and the extract was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed [PLC; silica gel; $CHCl_3$–EtOAc (4:1)] to give compound (**9**) (0.22 g, 44%) as an oil; R_F 0.35 [$CHCl_3$–EtOAc (4:1)]; ν_{max}(neat) 1 765 and 1 650 cm^{-1}; δ_H 1.37 (6 H, t, *J* 7.0 Hz, Me), 1.56–2.22 (4 H, m, CH_2), 2.48–3.24 (2 H, m, lactone CH), 3.88–4.60 (4 H, m, OCH_2Me), 4.80–5.16 (1 H, m, OCH), and 5.60–6.40 (2 H, m, olefinic H).

The spectral data of compound (**9**) were consistent with those of an alternative sample of compound (**9**) synthesized as described below.

Reaction of Iodo Lactone (**5b** *and* **c**) *with DBU*.—A solution of an iodo lactone (**5**) (1 mmol) in dry benzene (7 ml) containing DBU (0.30 g, 2 mmol) was refluxed for 3 h. After aq. NH_4Cl had been added, the reaction mixture was extracted with $CHCl_3$, and the extract was washed with water and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed (PLC; silica gel; $CHCl_3$) to give products (**7**) and (**9**).

Compound (**7**) (0.22 g, 85%); oil; R_F 0.42 ($CHCl_3$); ν_{max}(neat) 1 790 and 1 635 cm^{-1}; δ_H 1.36 (6 H, t, *J* 7.0 Hz, Me), 1.62 (3 H, s, C=CMe*Me*), 1.72 (3 H, s, C=C*Me*Me), 2.72–3.80 (3 H, m, lactone CH_2 and CH), and 3.80–4.60 (4 H, m, OCH_2Me); *m/z* 262 (M^+).

Compound (**9**) (0.21 g, 76%).

Hydrogenation of Compound (**9**).—Hydrogenation of compound (**9**) (0.33 g, 1.2 mmol) was accomplished in 5 h in ethanol (10 ml) over Pd–C (10%; 30 mg) to give the *lactone* (**10**) (0.31 g, 94%) as an oil; R_F 0.42 (CH_2Cl_2); ν_{max}(neat) 1 765 cm^{-1}; δ_H 1.37 (6 H, t, *J* 7.0 Hz, Me), 1.25–2.32 (8 H, m, CH_2), 2.32–3.16 (2 H, m, lactone CH), 3.80–4.60 (4 H, m, OCH_2Me), and 4.60–5.00 (1 H, m, OCH) (Found: M^+, 276.1124. $C_{12}H_{21}O_5P$ requires *M*, 276.1126).

Reduction of the Iodo Lactone (**5c**) *with Tributyltin Hydride*.—To a solution of compound (**5c**) (5.55 g, 13.8 mmol) and AIBN (0.45 g, 2.74 mmol) in dry THF (50 ml) at room temperature was added Bu_3SnH (8.03 g, 27.6 mmol). The mixture was refluxed for 7 h. After evaporation of THF, the residue was chromatographed on silica gel with CH_2Cl_2 as eluant to give lactone (**10**) (3.76 g, 99%).

Reduction of the Seleno Lactone (**6c**) *with Tributyltin Hydride*.—The reaction was carried out as described above, with seleno lactone (**6c**) (0.52 g, 1.21 mmol), AIBN (0.04 g, 0.24 mmol), and Bu_3SnH (0.70 g, 2.42 mmol). After similar work-up, the lactone (**10**) was obtained (0.28 g, 84%).

General Procedure for the Synthesis of α-Methylene-γ-lactones (**11**)–(**18**) *from α-Diethoxyphosphoryl-γ-lactones* (**5c** *and* **d**), (**6c** *and* **d**), and (**7**)–(**10**) *with Paraformaldehyde*.—To a solution of an *in situ* generated α-diethoxyphosphoryl-γ-lactone carbanion from an α-diethoxyphosphoryl-γ-lactone (1 mmol) and NaH (1.1 mmol) in dry THF (10 ml) at room temperature during 0.5 h was added paraformaldehyde (0.06 g, 2 mmol). The mixture was heated at reflux for 3 h. After evaporation of THF, the residue was chromatographed (PLC; silica gel; benzene) to give pure α-methylene-γ-lactones (**11**)–(**18**). The yields of the products are summarized in Table 2. The products (**11**)–(**18**) had the following properties.

Compound (**11**) oil; ν_{max}(neat) 1 760–1 780 and 1 660 cm^{-1}; δ_H 1.20–2.44 (6 H, m, CH_2), 3.00–3.52 (1 H, m, CH), 3.76–4.28 (1 H, m, CHI), 4.77 (1 H, t, *J* 7.1 Hz, OCH), 5.57 (1 H, d, *J* 2.7 Hz, C=C*H*H), and 6.25 (1 H, d, *J* 2.7 Hz, C=CH*H*); *m/z* 278 (M^+).

Compound (**12**) oil; ν_{max}(neat) 1 750–1 760 and 1 660 cm^{-1}; δ_H 1.00–2.40 (6 H, m, CH_2), 2.68–3.52 (2 H, br, CH and CHSe), 4.47 (1 H, t, *J* 6.8 Hz, OCH), 5.51 (1 H, d, *J* 2.4 Hz, C=C*H*H), 6.19 (1 H, d, *J* 2.4 Hz, C=CH*H*), and 6.88–8.00 (5 H, m, Ph) (Found: M^+, 308.0303. $C_{15}H_{16}O_2Se$ requires *M*, 308.0314).

Compound (**13**) oil; R_F 0.50 [EtOAc–hexane (1:4)]; ν_{max}(neat) 1 780 and 1 660 cm^{-1}; δ_H 1.61 (3 H, s, Me), 1.75 (3 H, s, Me), 3.50 (2 H, s, CH_2), 5.69 (1 H, t, *J* 2.6 Hz, C=C*H*H), and 6.30 (1 H, t, *J* 3.1 Hz, C=CH*H*) (Found: C, 69.2; H, 7.3%; M^+, 138.0663. Calc. for $C_8H_{10}O_2$: C, 69.55; H, 7.3%; *M* 138.0681).

Compound (**14**) oil; R_F 0.65 (benzene); ν_{max}(neat) 1 760 and 1 650 cm^{-1}; δ_H 1.74 (3 H, s, Me), 2.32–3.40 (2 H, m, CH_2), 4.60–5.20 (3 H, m, OCH and CH_2=CMe), 5.66 (1 H, t, *J* 2.4 Hz, C=C*H*H), and 6.24 (1 H, t, *J* 2.8 Hz, C=CH*H*) (Found: C, 69.2; H, 7.25%; M^+, 138.0696).

Compound (**15**)[6b] oil; R_F 0.30 (benzene); ν_{max}(neat) 1 765 and 1 655 cm^{-1}; δ_H 1.48–2.40 (4 H, m, CH_2), 2.92–3.40 (1 H, m, CH), 4.68–5.08 (1 H, m, OCH), 5.62 (1 H, d, *J* 2.4 Hz, C=C*H*H), 5.76–6.12 (2 H, m, CH=CH), and 6.23 (1 H, d, *J* 2.4 Hz, C=CH*H*) (Found: C, 72.0; H, 6.9%; M^+, 150.0717. Calc. for $C_9H_{10}O_2$: C, 72.0; H, 6.7%; *M*, 150.0618).

Compound (**16**)[6a,c] oil; R_F 0.35 (benzene); ν_{max}(neat) 1 760 and 1 660 cm^{-1}; δ_H 1.0–2.20 (8 H, m, CH_2), 2.72–3.28 (1 H, m, CH), 4.20–4.80 (1 H, m, OCH), 5.52 (1 H, d, *J* 2.3 Hz, C=C*H*H), and 6.18 (1 H, d, *J* 2.3 Hz, C=CH*H*) (Found: C, 70.7; H, 8.1%; M^+, 152. Calc. for $C_9H_{12}O_2$: C, 71.0; H, 8.0%; *M*, 152).

Compound (**17**) oil; ν_{max}(neat) 1 750–1 770 and 1 650 cm^{-1}; δ_H 1.00–2.80 (8 H, m, CH_2), 2.88–3.60 (1 H, br, CH), 4.00–4.60 (1 H, m, CHI), 4.85 (1 H, t, *J* 8.4 Hz, OCH), 5.63 (1 H, d, *J* 2.4 Hz, C=C*H*H), and 6.26 (1 H, d, *J* 2.4 Hz, C=CH*H*) (Found: M^+, 291.9994. $C_{10}H_{13}IO_2$ requires *M*, 291.9962).

Compound (**18**) oil; R_F 0.6 [EtOAc–hexane (1:7)]; ν_{max}(neat) 1 750–1 760 and 1 650 cm^{-1}; δ_H 1.06–2.44 (8 H, m, CH_2), 3.0–4.76 (2 H, br, CH and C*H*SePh), 4.69 (1 H, t, *J* 8.0 Hz, OCH), 5.59 (1 H, d, *J* 2.4 Hz, C=C*H*H), 6.28 (1 H, d, *J* 2.4 Hz, C=CH*H*), and 7.0–7.80 (5 H, m, Ph); *m/z* 321 (M^+).

Oxidation of Seleno Lactones (**6b** *and* **c**), (**12**), *and* (**18**).—To a solution of a seleno lactone (1 mmol) in CH_2Cl_2 (10 ml) at −78 °C was added a solution either of H_2O_2 (30%; 0.5 ml) in water (5 ml) or of *m*-chloroperbenzoic acid (0.26 g, 1.5 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred at this temperature for 1 h, and at room temperature for 4 h. After conventional work-up, the residue was chromatographed (PLC; silica gel; diethyl ether or benzene) to give products (**8**), (**9**), (**15**), and (**19**).

Compound (**8**) (0.17 g, 64%); oil; R_F 0.37 (Et_2O); ν_{max}(neat) 1 770 and 1 650 cm^{-1}; δ_H 1.29 (6 H, t, *J* 7.0 Hz, Me), 1.70 (3 H, s, C=CMe), 2.20–3.60 [3 H, m, P(O)CHCH_2], 3.68–4.48 (4 H, m, OCH_2Me), and 4.48–5.32 (3 H, m, OCH and olefinic H).

Compound (**9**) (0.15 g, 58%).

Compound (**15**) (0.89 g, 59%).

Compound (**19**) (0.13 g, 80%); oil R_F 0.35 (benzene); ν_{max}(neat) 1 750–1 760 and 1 650 cm^{-1}; δ_H 1.32–2.52 (6 H, m, CH_2), 2.80–3.52 (1 H, m, CH), 5.16–5.80 (3 H, m, OCH and CH=CH), 5.62 (1 H, d, *J* 2.6 Hz, C=C*H*H), and 6.25 (1 H, d, *J* 2.6 Hz, C=CH*H*) (Found: C, 72.9; H, 7.4%; M^+, 164.0835. Calc. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.4%; *M*, 164.0836),

Reaction of Anion (**1**) *with* 7-*Bromo*-1,4a-*dimethyl*-1,2,3,4,4a,5,6,7-*octahydronaphthalene* (**20**). The reaction was carried out at room temperature for 12 h with ethyl (diethoxyphosphoryl)acetate (11.21 g, 50 mmol), NaH (60% in oil; 2.20 g, 55 mmol), and the bromide (**20**) (50 mmol). After work-up, the product (**21**) was obtained (15.30 g, 85%) as an oil; ν_{max}(neat) 1 730 and 1 640 cm^{-1}; δ_H 0.60–2.28 (26 H, m, Me, CH_2, and CH), 2.28–3.40 (2 H, m, CH), 3.60–4.60 (6 H, m, OCH_2), 5.10 (0.4 H, br, olefinic H), and 5.46 (0.6 H, br, olefinic H); *m/z* 386 (M^+).

Hydrolysis of Ester (**21**).—A solution of ester (**21**) (1.15 g, 2.98 mmol) in EtOH–water (2:1; 27 ml) containing NaOH (1.15 g, 10 mol equiv.) was stirred at room temperature overnight. After work-up, the *acid* (**22**) was obtained as an oil (1.02 g, 96%); ν_{max}(neat) 1 720 cm^{-1}; δ_H 0.67–2.33 (23 H, m, Me, CH_2, and CH), 2.40–3.20 (2 H, m, CH), 3.80–4.53 (4 H, m, OCH_2), 5.16 (0.4 H, br, olefinic H), 5.44 (0.6 H, br, olefinic H), and 9.80 (1 H, s, OH) (Found: C, 60.2; H, 8.8. Calc. for $C_{18}H_{31}O_5P$: C, 60.3; H, 8.7%).

Iodolactonization of Acid (**22**).—The reaction was carried out at room temperature for 72 h, as described above for compounds (**4**), with the reactant acid (**22**) (1.48 g, 4.13 mmol), KI (6.17 g, 37.17 mmol), and I_2 (3.14 g, 12.39 mmol) in water–THF (6:5; 44 ml) containing $NaHCO_3$ (0.69 g, 8.27 mmol). After similar work-up, the residue was chromatographed [PLC; silica gel; Et_2O–hexane (1:1)] to give lactone (**24**) (0.69 g, 47%) and unchanged acid (**22**) (0.62 g, 42% recovery).

Lactone (**24**) was an oil; R_F 0.25 [Et_2O–hexane (1:1)]; ν_{max}(neat) 1 760 and 1 640 cm^{-1}; δ_H 0.80–2.20 (22 H, m, Me and CH_2), 2.50–3.08 (2 H, m, CH), 3.88–4.48 (4 H, m, OCH_2), and 5.67 (1 H, d, *J* 5.13 Hz, OCH); *m/z* 357 (M^+).

Synthesis of Frullanolide (**25**).—The reaction was carried out at 0 °C for 1 h, as described above for the preparation of compounds (**11**)–(**18**), with the phosphoryl lactone (**24**) (0.11 g, 0.31 mmol), NaH (60% in oil; 14 mg, 0.34 mmol), and paraformaldehyde (19 mg, 0.62 mmol) in dry THF (5 ml). After similar work-up, the residue was chromatographed [PLC; silica gel; EtOAc–hexane (1:7)] to give frullanolide (**25**) (0.07 g, 97%), m.p. 92–93 °C (lit.,[8e] 93–93.5 °C); ν_{max}(KBr) 1 760, 1 665, and 1 645 cm^{-1}; δ_H 1.08 (3 H, s, Me), 1.76 (3 H, s, Me), 1.15–1.95 (8 H, m, CH_2), 1.95–2.20 (2 H, m, CH_2), 2.68–3.20 (1 H, m, CH), 5.26 (1 H, d, *J* 5.71 Hz, OCH), 5.58 (1 H, d, *J* 1.02 Hz, olefinic H), and 6.15 (1 H, d, *J* 1.02 Hz, olefinic H) (Found: C, 77.2; H, 8.7%; M^+, 232.1502. Calc. for $C_{15}H_{20}O_2$: C, 77.5; H, 8.7%; *M*, 232.1463).

Acknowledgements

We are grateful for financial support of this work by a Grant-in-Aid for Scientific Research (62550615) and by a Grant-in-Aid for Scientific Research on Priority Areas (63607523) from the Japan Ministry of Education, Science and Culture.

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Paper 9/05153H
Received 4*th December* 1989
Accepted 12*th April* 1990