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A New Synthesis of γ-Lactones with α,β-Fused Ring Systems Using α-Diethoxyphosphinyl-$\Delta^{\alpha,\beta}$-butenolides

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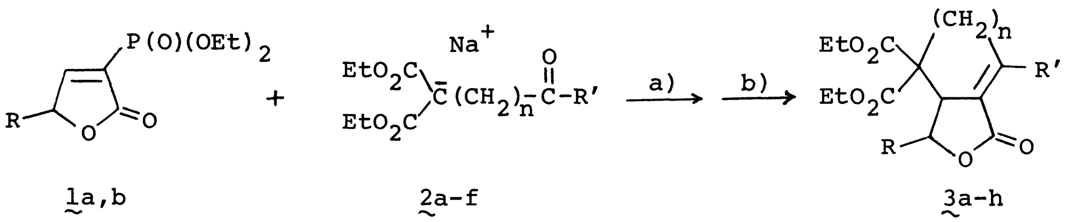
The intramolecular Wittig-Horner reaction of α-diethoxyphosphinyl-$\Delta^{\alpha,\beta}$-butenolides with various nucleophilic reagents containing the carbonyl group produced α,β-carbocyclic fused-γ-lactones in moderate yields.

There have been known many naturally occurring sesquiterpene γ-lactones with α,β-fused ring systems,[1] which attracted much interest due in large part to their biological activities. In comparison with β,γ-fused lactones, synthetic methods for the construction of α,β-fused-γ-lactone systems have not been well developed.[2] We have recently reported a new synthesis of α-diethoxyphosphinyl-$\Delta^{\alpha,\beta}$-butenolide (1a) and its synthetic application to α,β-difunctionalized γ-lactones such as lignans.[3] In the present paper, we report the successful utilization of α-diethoxyphosphinyl-$\Delta^{\alpha,\beta}$-butenolides as versatile reagents for



(1)

1a,b 2a-f 3a-h

1a: R= H 1b: R= Me

a) THF, -78 °C, 1 h. b) -78 °C—room temp, 9 h, and then reflux, 2 h.

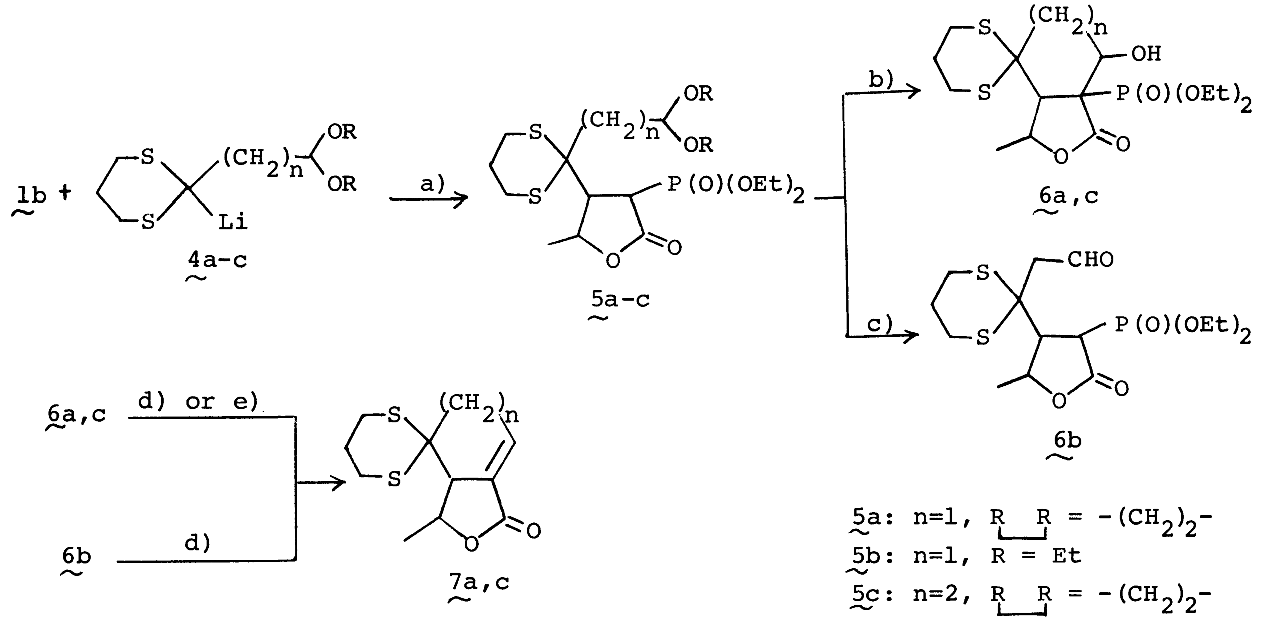
efficient construction of α,β-carbocyclic fused-γ-lactones. The reaction of $\Delta^{\alpha,\beta}$-butenolides 1a,b[4)] with the carbanions 2a-f, generated in-situ from diethyl-2-oxoalkyl- and 3-oxoalkylmalonates and 1.1 equiv. of sodium hydride in THF, at -78 °C to room temperature for 9 h and at reflux for 2 h afforded the expected α,β-carbocyclic fused-γ-lactones 3a-h[5)] in moderate yields (Eq. 1)(Table 1).

Table 1. Synthesis of α,β-carbocyclic fused-γ-lactones 3

3	n	R	R'	Yield/%[a)]	3	n	R	R'	Yield/%[a)]
3a	1	H	Me	24	3e[b)]	2	H	Me	46
3b	1	Me	Me	78	3f	2	Me	Me	59
3c	1	H	Ph	48	3g	2	H	H	62
3d	1	Me	Ph	62	3h	2	Me	H	54

a) Isolated yield. b) See Ref. 3.

Similar reaction of the butenolide 1b with 2-lithio-2-(1',3'-dioxolan-2'-yl)methyl-(4a), -2-(2',2'-diethoxyethyl)-(4b), and -2-[β-(1',3'-dioxolan-2'-yl)ethyl]-1,3-dithianes (4c), followed by quenching with aqueous NH_4Cl, provided

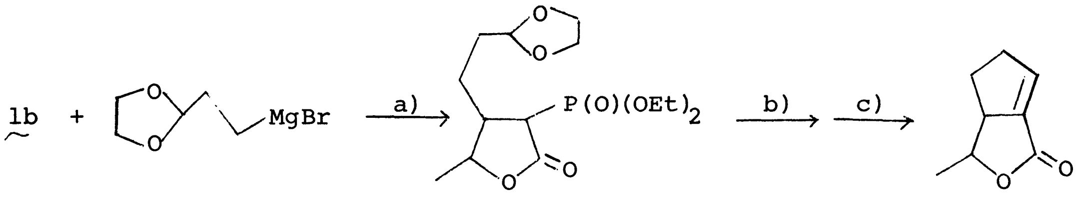


5a: n=1, $\underbrace{R\ \ R} = -(CH_2)_2-$
5b: n=1, R = Et
5c: n=2, $\underbrace{R\ \ R} = -(CH_2)_2-$
6a, 7a: n=1
6c, 7c: n=2

a) -78 °C, 3 h, -78 °C—room temp, 9 h.
b) 1 mol dm^{-3} HCl/THF (1/1), reflux, 5 h.
c) p-TsOH (0.1 equiv.)/aq acetone, reflux, 5 h.
d) NaH/THF, room temp, 3 h.
e) TLC (SiO_2, hexane/ethyl acetate = 2/1)

Scheme 1.

the corresponding Michael adducts **5a**-c in 55-58% yields. Interestingly, hydrolysis of the adducts **5a**-c with 1 M (1 M = 1 mol dm^{-3}) hydrochloric acid in THF at reflux for 5 h gave the bicyclic phosphonates **6a**,c in quantitative yields, while similar treatment of **5b** in aqueous acetone containing p-TsOH (0.1 equiv.) led to the expected phosphonate **6b** (63% yield).6) The structure of **6a**,c were determined on the basis of their IR, and ^{1}H and ^{13}C NMR spectra.6) The phosphonates **6a** and **6c**, upon treatment with preparative TLC (silica gel, hexane/ethyl acetate = 2/1), were unexpectedly transformed into the bicyclic γ-lactones7) **7a** and **7c** in 83% and 64% yields. Alternatively, the lactone **7a** could be also produced in 53% and 65% yields from respective treatments of **6a** and **6b** with sodium hydride in THF at room temperature for 3 h (Scheme 1). Moreover, the reaction of (1,3-dioxolan-2-yl)-ethylmagnesium bromide with **1b** under similar conditions provided the Michael adduct **6d** (63% yield), followed by acidic hydrolysis and the intramolecular Wittig-Horner reaction to give the fused lactone **7d**7) in 54% yield (Eq. 2).



(2)

6d **7d**

a) -78 °C, 4 h. b) 1 M HCl/THF (1/1), reflux, 5 h. c) NaH/THF, room temp, 5 h.

This methodology using diethoxyphosphinyl-α,β-butenolides could be said to provide a remarkably simple route to α,β-carbocyclic fused γ-lactones. We are pursuing synthetic applications of the products described above.

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References

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2) C. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac, and C. T. White, "The Total Synthesis of Natural Products," ed by J. ApSimon, John-Willy & Sons, New York (1983), Vol. 5, p. 172, 404.

3) T. Minami, Y. Kitajima, and T. Chikugo, Chem. Lett., 1986, 1229.

4) The butenolide **1b** was prepared in 93% yield from α-diethoxyphosphinyl-γ-valerolactone according to the established method.[3)] The butenolide **1b** is rather stable than **1a**.

5) **3a**: oil; IR (neat) 1760, 1730, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.27(t, J=7.1 Hz, 6H, Me), 2.06(br s, 3H, Me), 3.20-3.44(br d, 2H, CH_2), 3.84(d, J=1.5 Hz, 1H, CH), 4.00-4.44(q, J=7.1 Hz, 4H, $O\underline{CH_2}CH_3$), 4.51(d, J=4.0 Hz, 2H, OCH_2); HRMS Found : m/z 282.1097, Calcd for $C_{14}H_{18}O_6$; M^+, m/z 282.1102 .

3g: oil; IR (neat) 1760, 1730, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 and 1.35(t, J=7.1 Hz, 6H, Me), 1.72-2.70(m, 4H, CH_2), 3.08-3.64(m, 1H, CH), 4.00-4.44(2q, J=7.1, 7.1 Hz, 4H, $O\underline{CH_2}CH_3$), 4.55(s, 1H, one of OCH_2), 4.70(d, J=1.0 Hz, one of OCH_2), 6.79(t, J=3.5 Hz, olefinic H) ; ^{13}C NMR ($CDCl_3$) δ 13.9, 24.0, 28.6, 40.7, 54.0, 61.5, 61.8, 68.8, 126.5, 134.8, 167.7, 168.8, 170.0 ; HRMS Found : m/z 282.1066, Calcd for $C_{14}H_{18}O_6$; M^+, m/z 282.1102 . All the other products **3a-f**,**h** similarly gave satisfactory spectral data (IR, ^{1}H and ^{13}C NMR, Exact mass).

6) **6a**: oil; IR (neat) 3400 (OH), 1770 cm^{-1} (C=O) ; ^{1}H NMR ($CDCl_3$) δ 1.36(t, J=7.0 Hz, 6H, Me), 1.56(d, J=6.6 Hz, 3H, $>CH\underline{Me}$), 1.80-2.30(m, 5H, CH_2, CH), 2.50-3.32 (m, 5H, SCH_2, OH), 3.90-4.50(m, J=7.0 Hz, 4H, $O\underline{CH_2}CH_3$), 4.50-5.30(m, 2H, OCH) ; MS m/z 396 (M^+).

6b: oil; IR (neat) 1770 (lactone C=O), 1720 cm^{-1} (CHO) ; MS m/z 396 (M^+).

7) **7a**: oil; IR (neat) 1755, 1650 cm^{-1} ; ^{1}H NMR ($CDCl_3$) δ 1.56(d, J=5.7 Hz, 3H, Me), 1.70-2.30(m, 2H, CH_2), 2.60-3.16(m, 4H, SCH_2), 3.30-3.70(m, 3H, CH_2, CH), 4.64-5.16(m, 1H, $O\underline{CH}Me$), 6.51(q, J=5.7 Hz, 1H, olefinic H) ; HRMS Found : m/z 242.0427, Calcd for $C_{11}H_{14}O_2S_2$; M^+, m/z 242.0435.

7d: oil; IR (neat) 1765, 1650 cm^{-1} ; ^{1}H NMR ($CDCl_3$) δ 1.57(d, J=6.1 Hz, 3H, Me), 1.70-3.50(m, 5H, CH_2, CH), 3.92-4.48(m, 1H, $O\underline{CH}Me$), 6.61(q, J=2.6 Hz, 1H, olefinic H).

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