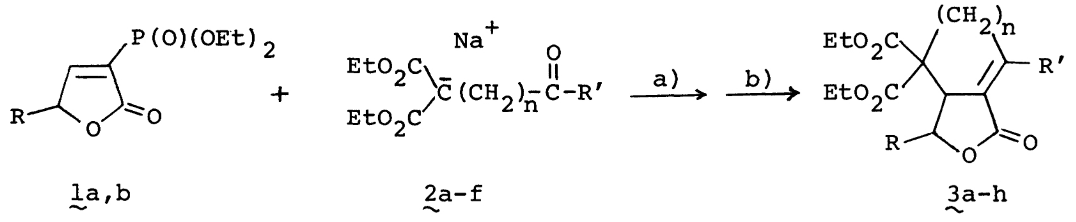
CHEMISTRY LETTERS, pp. 2369-2372, 1987.

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

Toru MINAMI,* Kazushi WATANABE, Tsuguhiko CHIKUGO,
and Yoshiyuki KITAJIMA
Department of Industrial Chemistry, Kyushu Institute of Technology,
Sensui-cho, Tobata, Kitakyushu 804

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: R= H 1b: R= Me

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

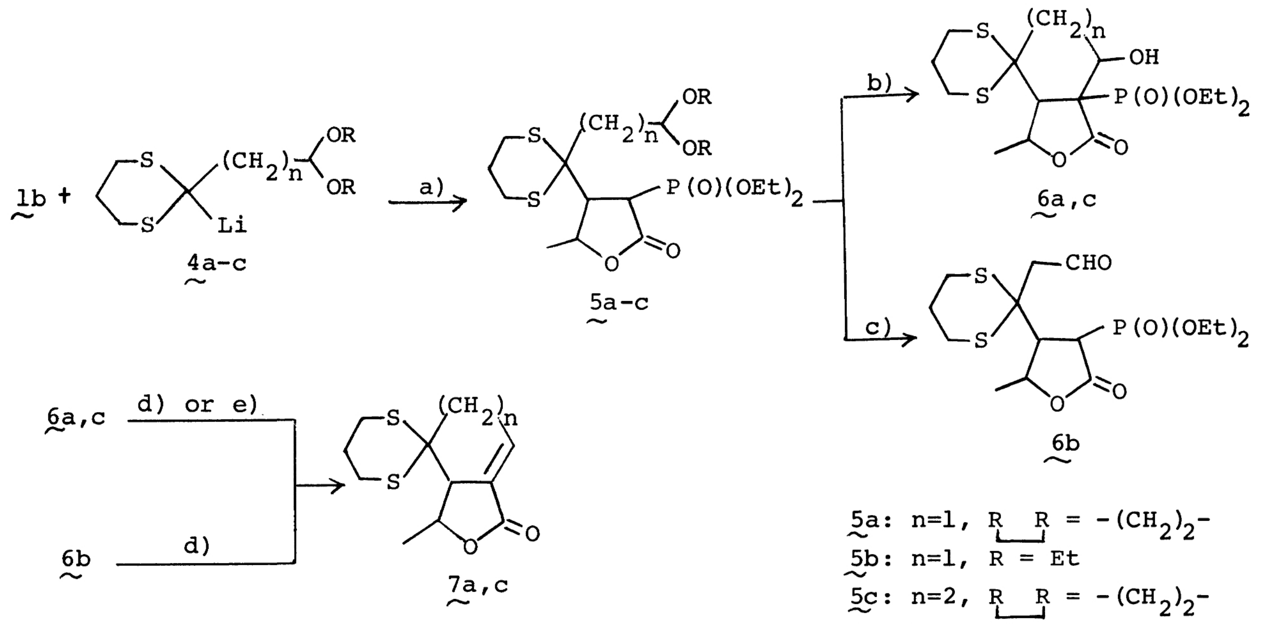
efficient construction of α,β-carbocyclic fused-γ-lactones. The reaction of $\Delta^{\alpha,\beta}$-butenolides 1a,b[4] with the carbanions 2a-f, generated in-situ from diethyl-2-oxoalkyl- and 3-oxoalkylmalonates and 1.1 equiv. of sodium hydride in THF, at -78 °C to room temperature for 9 h and at reflux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

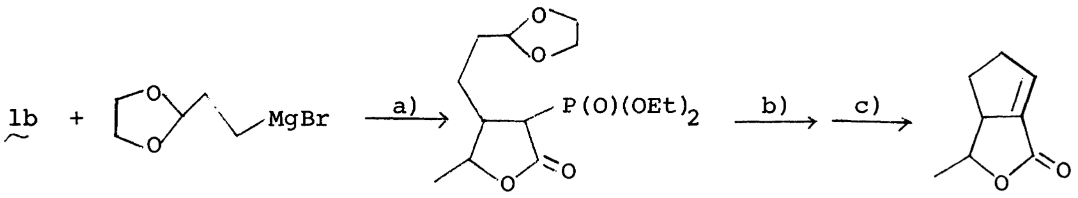


5a: n=1, R R = $-(CH_2)_2-$
5b: n=1, R = Et
5c: n=2, R R = $-(CH_2)_2-$
6a, 7a: n=1
6c, 7c: n=2

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 7d7) in 54% yield (Eq. 2).



6d 7d (2)

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.

We are grateful for financial support of this work by a Grant-in-Aid for General Scientific Research (No. 62550615) from the Japan Ministry of Education, Science and Culture and by the Yoshida Society for Promotion of Science.

References

1) For example : T. D. Devon and A. I. Scott, "Handbook of Naturally Occurring Compound," Academic Press, New York (1972), Vol. 2, p. 154.

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}; ^1H 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, $O\underline{CH}_2CH_3$), 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}; ^1H 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, $O\underline{CH}_2CH_3$), 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, ^1H and ^{13}C NMR, Exact mass).

6) **6a**: oil; IR (neat) 3400 (OH), 1770 cm^{-1} (C=O) ; ^1H 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, $O\underline{CH}_2CH_3$), 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} ; ^1H 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} ; ^1H 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).

(Received September 21, 1987)