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α-Diethoxyphosphinyl-γ-butenolide, a Versatile Reagent for the Synthesis of α,β-Difunctionalized γ-Lactones

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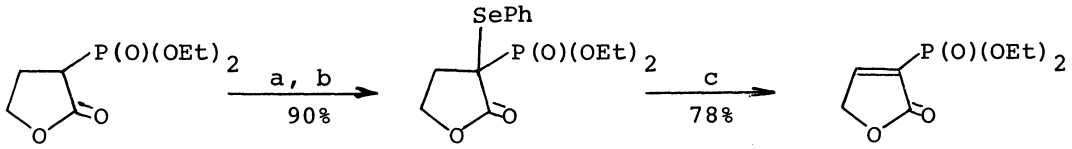
α-Diethoxyphosphinyl-γ-butenolide (2) was synthesized in good yield by phenylselenenylation of an α-diethoxyphosphinyl-γ-butyrolactone carbanion and subsequent oxidative elimination of the phenylseleno residue. The butenolide 2 underwent the Michael addition of various nucleophiles to generate the phosphoryl-stabilized carbanions, which reacted with carbonyl compounds to give α,β-difunctionalized γ-butyrolactones, lignans, and a γ-butyrolactone annelated compound.

There has been recently intense interest in developing synthetic routes to naturally occurring compounds having the γ-butyrolactone moiety, due in large part to their biological activities.[1] We have previously reported a convenient method for introduction of γ-butyrolactone moiety to organic molecules using α-diethoxyphosphinyl-γ-butyrolactone (1).[2] In the present paper, we report the synthesis of a versatile reagent, α-diethoxyphosphinyl-γ-butenolide (2) and its synthetic application to α,β-difunctionalized γ-lactones, and lignans such as savinin and its analogues.

As shown in Scheme 1, α-diethoxyphosphinyl-γ-butenolide (2) was successfully synthesized in 78% yield by oxidative elimination of the phenylseleno moiety in α-diethoxyphosphinyl-α-phenylseleno-γ-butyrolactone (3), which was prepared in 90% yield from the reaction of an α-diethoxyphosphinyl-γ-butyrolactone carbanion with phenylselenenyl bromide. The structure of 2 was assigned on the basis of its spectral data: IR (neat) 1755 and 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (t, J=7.10 Hz, 6H, CH_3), 3.80-4.60 (quint., J=7.10 Hz, 4H, $O\underline{CH_2}CH_3$), 5.02 (br, 2H, OCH_2), and 8.17 (br d, J=9.52 Hz, 1H, olefinic H). Similar to vinylphosphonates,[3] the butenolide

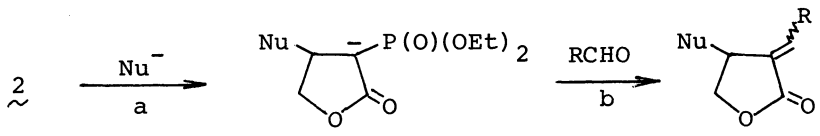


1 3 2

a) NaH, dry THF, 60 °C, 1 h; b) PhSeBr, -75 °C, 1 h→rt, 1 h
b) 30% H_2O_2, CH_2Cl_2, -10 °C—0 °C, 3 h

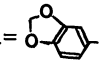
Scheme 1.

2 can be expected to undergo the Michael addition of various nucleophiles to generate the phosphoryl-stabilized carbanions, which are trapped with aldehydes to give β-functionalized α-ylidene-γ-butyrolactones. Thus, treatment of 2[4] with t-butyl lithioacetate, followed by the reaction of aldehydes, led to α-ylidene-β-(t-butoxycarbonylmethyl)-γ-lactones 4a-c[5] in 36-42% yields. The reaction of 2 with lithium dibutylcuprate(I) and benzaldehyde similarly gave a functionalized lactone 4d[5] in 45% yield.



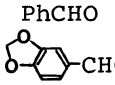
4a-d

a) THF, -75 °C, 1 h
b) -75 °C, 1 h→rt, 1 h→reflux, 3 h

4a: Nu=$CH_2CO_2{}^tBu$; R=Ph
4b: Nu=$CH_2CO_2{}^tBu$; R= 
4c: Nu=$CH_2CO_2{}^tBu$; R=Bu
4d: Nu=Bu; R=Ph

Scheme 2.

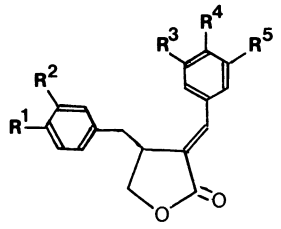
Table 1. Synthesis of α,β-Difunctionalized γ-Lactones

Nucleophile	Aldehyde	Product	Yield/%	E:Z[b]
$LiCH_2CO_2{}^tBu$	PhCHO	4a	42	3:1
$LiCH_2CO_2{}^tBu$		4b	38	3:1
$LiCH_2CO_2{}^tBu$	BuCHO	4c	36	2:3
Bu_2CuLi	PhCHO	4d	45	---

a) Isolated yield. No attempt to optimize yields has been made.
b) Determined by ^1H and ^{13}C NMR.

Accordingly, this methodology was applied to the construction of the basic lignan skeleton. The reaction of the phosphonate carbanion, generated from the Michael addition of piperonylmagnesium chloride to 2 in the presence of a catalytic amount

of copper(I) iodide, with piperonal under similar conditions produced a 46% yield of (±)-Savinin (4f)[mp 154-156 °C (lit.,[6] mp 156 °C); IR (KBr) 1740 and 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30-3.20 (m, 2H), 3.40-4.00 (br, 1H), 4.25 (d, J=4.10 Hz, 2H), 5.93 (s, 2H), 6.04 (s, 2H), and 6.60-7.60 (m, 7H)].



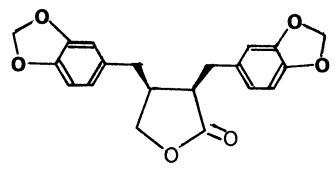
4e-h

Table 2. Synthesis of Lignans

Product[a]	R^1	R^2	R^3	R^4	R^5	Yield/%[b]
4e	H	H	H	H	H	82
4f	$-OCH_2O-$		$-OCH_2O-$		H	46
4g	$-OCH_2O-$		OMe	OMe	OMe	57
4h	OMe	OMe	OMe	OMe	OMe	21

a) A single stereoisomer on the basis of their ^1H and/or ^{13}C NMR data.

b) Isolated yield.



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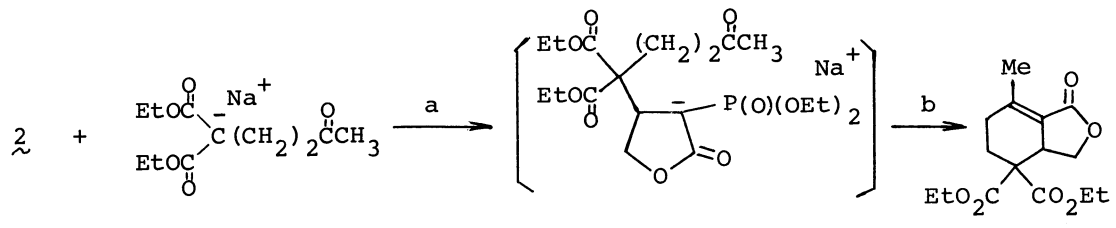
Similar treatment of 2 with benzylmagnesium chlorides and aromatic aldehydes led to the corresponding lignan derivatives 4e,g,h[7] in 21-82% yields (Table 2). Hydrogenation of 4f in ethyl acetate over 10% Pd-C at low hydrogen pressure (2 atm) gave (±)-isohinokinin (5)[8] (84% yield) [mp 115 °C (lit.,[6,8] mp 115-116 °C); IR 1770 cm^{-1}].

Furthermore, in an attempt to develop a short and efficient approach to sesquiterpene lactone construction, we have examined to utilize the butenolide 2 for the one-step synthesis of γ-butyrolactone annelated compounds.

The intramolecular Wittig-Horner reaction of the carbanion 7, generated from



6 7 8

a) THF, -75 °C, 1 h

b) reflux, 3 h

Scheme 3.

similar treatment of 2 with the carbanion 6, gave the hoped-for γ-butyrolactone annelated compound 8[9] in 46% yield.

Thus, α-diethoxyphosphinyl-γ-butenolide (2) can serve as a versatile reagent not only for the synthesis of α,β-difunctionalized γ-lactones and lignans, but for the γ-butyrolactone annelation. Further studies are in progress.

References

1) See for examples: P. A. Grieco, Synthesis, 1975, 67 and references cited therein; Y. S. Rao, Chem. Rev., 76, 625 (1976); R. S. Ward, Chem. Soc. Rev., 11, 75 (1982).
2) T. Minami, I. Niki, and T. Agawa, J. Org. Chem., 39, 3236 (1974); T. Minami, M. Matsumoto, H. Suganuma, and T. Agawa, ibid., 43, 2149 (1978).
3) T. Minami, H. Suganuma, and T. Agawa, Chem. Lett., 1978, 285; T. Minami, K. Nishimura, I. Hirao, H. Suganuma, and T. Agawa, J. Org. Chem., 47, 2360 (1982).
4) The butenolide 2 was used without purification due to susceptibility to polymerization even allowing to stand at room temperature.
5) All the new compounds gave satisfactory, spectral data and analytical data (±0.4 % for C, H). Physical and spectral data for the selected compounds are as follows: 4a [a 3:1 mixture of (E)- and (Z)-4a]: mp 133-135 °C; ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.20-2.80 (m, 2H), 3.80-4.60 (br, 3H), 6.80-7.00 [br, 0.25H, (E)-H of HC=C-(CO)-], 7.20-7.60 (br, 5H), and 7.60-7.90 [br, 0.75H, (Z)-H of HC=C-(CO)-].
4c [a 2:3 mixture of (E)- and (Z)-4c]: oil; ^{1}H NMR ($CDCl_3$) δ 0.80-1.80 (m, 18H), 2.20-3.0 (m, 3H), 3.70-4.70 (m, 2H), 6.04-6.36 [dt, J=2.2, 7.8 Hz, 0.6H, (E)-H of HC=C-(CO)-], and 6.50-6.82 [dt, J=2.2, 7.8 Hz, 0.4H, (Z)-H of HC=C-(CO)-].
6) J. E. Batterbee, R. S. Burden, L. Crombie, and D. A. Whiting, J. Chem. Soc., C , 1969, 2470.
7) Although we cannot exclude the stereoisomeric Z-form, we tentatively assign the products the E-structure 4e,g,h since the reaction of the diethoxyphosphinyl-γ-butyrolactone carbanion with aromatic aldehydes led exclusively to E-isomers.[2]
4e: oil; ^{1}H NMR ($CDCl_3$) δ 2.28-3.30 (m, 2H), 3.60-4.10 (br, 1H), 4.26 (d, J=4.0 Hz, 2H), and 7.00-7.70 (m, 11H); ^{13}C NMR ($CDCl_3$) δ 37.8, 39.8, 69.7, 127.1, 128.5, 128.9, 129.1, 130.0, 134.1, 137.4, 137.9, and 172.3.
4g: mp 102-104 °C; ^{1}H NMR ($CDCl_3$) δ 2.32-3.24 (m, 2H), 3.60-3.90 (br, 1H), 3.88 (s, 9H), 4.20-4.40 (br, 2H), 5.92 (s, 2H), 6.40-6.80 (m, 5H), and 7.40-7.56 (br, 1H).
8) K. Yamashita and M. Matsui, Bull. Agr. Chem. Jpn., 22, 227 (1958).
5: ^{1}H NMR ($CDCl_3$) δ 2.00-3.10 (m, 5H), 3.56-4.20 (m, 3H), 6.67 and 6.76 (2s, 4H, $-OCH_2O-$), and 6.40-6.80 (m, 6H).
9) 8: pale yellow oil; IR (neat) 1720-1760 and 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J=7.0 Hz, 6H), 1.56 (s, 3H), 1.60-2.60 (m, 5H), 4.26 (q, J=7.0 Hz, 4H), and 5.02 (d, J=2.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 21.4, 28.1, 31.2, 56.5, 62.9, 71.2, 77.9, 131.7, 158.8, 167.2, and 167.5.

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