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CONVENIENT SYNTHESIS OF 5-ALKYLIDENE-2(5H)-FURANONES, 2(5H)-FURANONES AND 2-ETHOXYFURANS **

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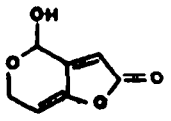
Abstract: Starting from enolizing 1,2-diketones 5 and (2,2-diethoxyvinylidene)triphenylphosphorane (2) or from 5 and (2,2-diethoxyvinyl)triphenylphosphonium tetrafluoroborate (6) the orthoesters 9 are prepared. 9 can be hydrolyzed under acidic conditions to give 5-alkylidene-2(5H)-furanones 10. Reaction of 1,2-hydroxyketones 11 and (2,2-diethoxyvinylidene)triphenylphosphorane (2) via Michael addition and Wittig reaction yields orthoesters 15, which can be hydrolyzed to give 2(5H)-furanones 16 and 2-ethoxyfurans 17 respectively.
A considerable variation of the substituents (R^4) can be achieved starting from 11 and (2,2-diethoxyvinyl)triphenylphosphonium tetrafluoroborates 12.

In numerous cases the intramolecular Wittig reaction has proven to be an excellent method for the synthesis of cyclic compounds /2/. In this connection the phosphacumulene ylides 1 /3/ and phosphaallene ylide 2 /4/ are of special interest, since, 1 and 2 with H-acidic compounds containing an extra carbonyl group, yield phosphoranes which subsequently undergo an intramolecular Wittig reaction. 2 is suitable for the preparation of 5-alkylidene-2(5H)-furanones /1,5/, whose parent compound, protoanemonin (3) /6/, has antibiotic activity. In addition, 2 is a good precursor for the synthesis of anellated 5-alkylidene-2(5H)-furanones /7/, which show the same connectivity as the well known antibiotic, patulin (4) /8/. This paper reports a considerable simplification and expansion of the procedure described earlier.

1: Y = O, S, NPh$_3$

2

3



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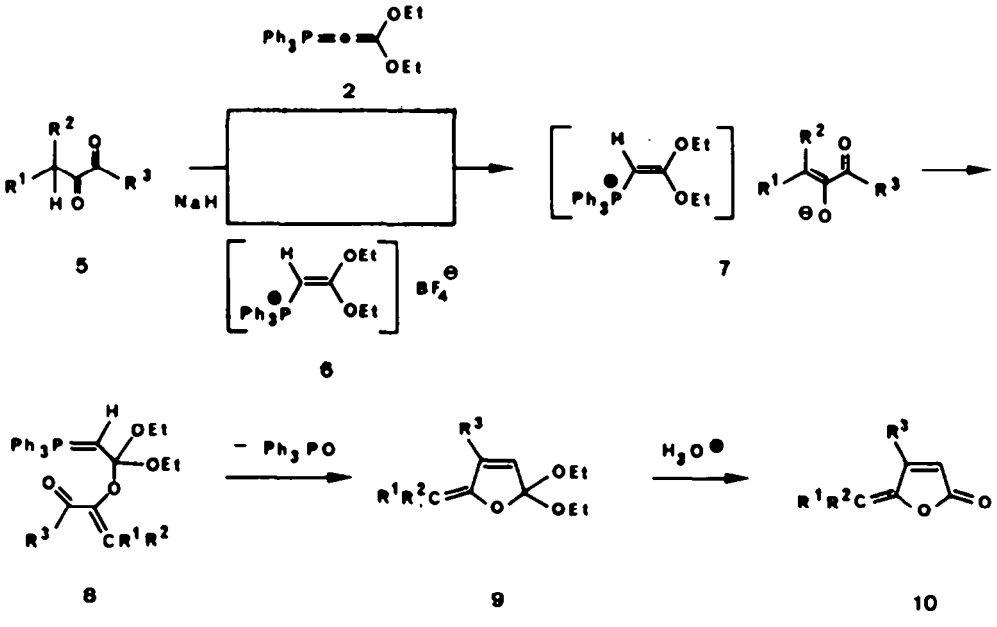
Reaction of the enolizing 1,2-diketones 5 and (2,2-diethoxyvinylidene)triphenylphosphorane (2) forms the corresponding phosphonium enolates 7. In the presence of sodium hydride the intermediates 7 can also be generated from the 1,2-diketones 5 and (2,2-diethoxyvinyl)triphenylphosphonium tetrafluoroborate (6). The phosphonium enolates 7 further react to give the phosphoranes 8 which, subsequently, in an intramolecular Wittig reaction, yield the orthoesters 9. Acidic hydrolysis of 9 gives 5-alkylidene-2(5H)-furanones 10.

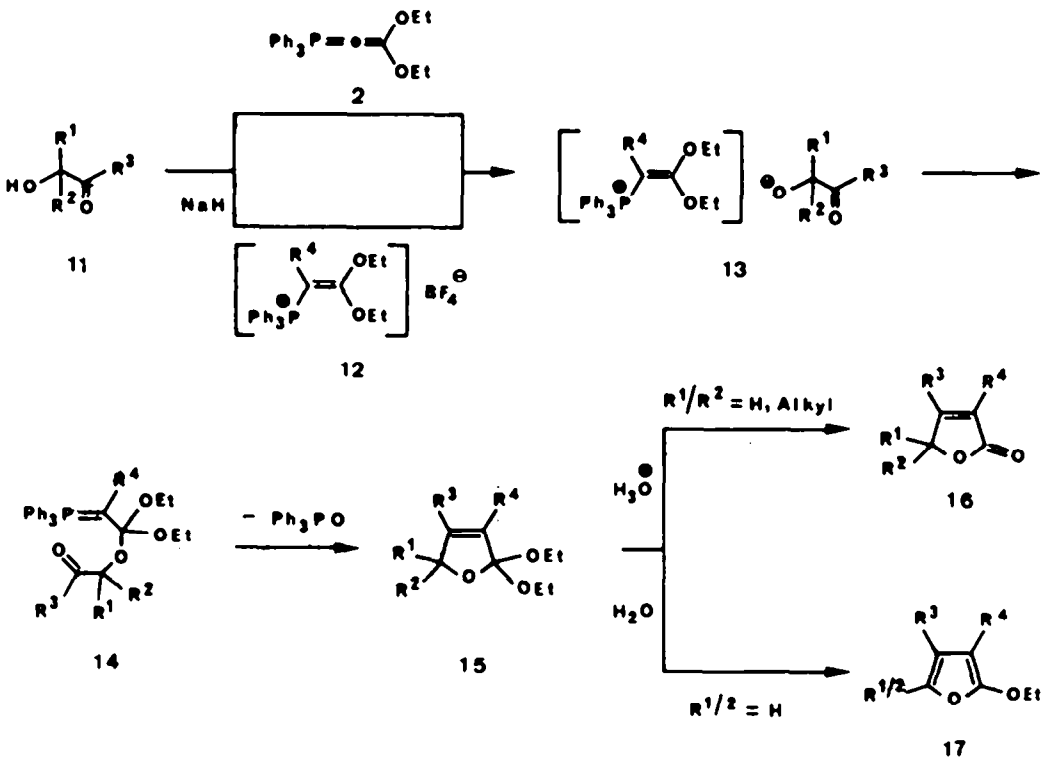


2 5 6 7 8 9 10

5, 7 - 10	R^1	R^2	R^3
a	H	Ph	Ph

5, 7 - 10	R^1	R^2	R^3
b	CH_3	CH_3	Ph

Phosphonium alcoholates 13 (R^4=H) /9/ are generated from the 1,2-hydroxyketones 11 and (2,2-diethoxyvinylidene)triphenylphosphorane (2). The substituent pattern in 13 can be substantially enlarged, starting from (2,2-diethoxyvinyl)triphenylphosphonium tetrafluoroborates 12 (R^4 = H corresponds to 6), 1,2-hydroxyketones 11 and sodium hydride. The phosphonium alcoholates 13 give the phosphoranes 14 spontaneously. In an intramolecular Wittig reaction the phosphoranes 14 cyclize to 2,2-diethoxy-2,5-dihydrofurans 15.
Acidic hydrolysis of the orthoesters 15 in aqueous p-toluenesulphonic acid yields 2(5H)-furanones 16 /10/. Because of its many properties (phytotoxin, pheromone, analeptic, use in perfume industry), (+)-dihydroactinidiolide ((16d), overall yield 72%) is surely the most interesting of the examples given below /11/. A concise asymmetric synthesis starting from E-2,6-dimethylcyclohexanone and chiral lithium camphylamide yields (5S)-dihydroactinidiolide (16d) in 27% overall yield /12/. Hydrolysis of 15 at pH 7 leads to 2-ethoxyfurans 17 /13/ (data see table 1).



11 - 17	R^1	R^2	R^3	R^4
a	H	$-(CH_2)_4-$		$CH_2CO_2CH_3$
b	H	CH_3	CH_3	$CH_2CH{=}CH_2$

11 - 16	R^1	R^2	R^3	R^4
c		$-(CH_2)_5-$	CH_3	H
d	CH_3	$-(CH_2)_3C(CH_3)_2-$		H

Experimental Section

General Procedure for the Synthesis of Orthoesters 9 and 15:

Method A: Orthoesters 9

To a suspension of 0.3 g (12.5 mmol) sodium hydride and (2,2-diethoxyvinyl)triphenylphosphonium tetrafluoroborate (6) (12.5 mmol) in 150 ml THF, a solution of the corresponding diketone 5 (12.5 mmol) in 50 ml THF is added. After stirring for 1.5h and refluxing for 3h the solvent is evaporated. The residue is stirred with 70 ml of n-hexane for 3h. Filtration and bulb-to-bulb distillation (50-100°C/0.05 Torr) yield the orthoesters 9 as colourless, air-sensitive liquids. (Data see table 1).

Method B: Orthoesters 15

To a stirred suspension of 0.3 g (12.5 mmol) sodium hydride in 120 ml THF, is added a solution of the corresponding 2-hydroxyketone 11 (12.5 mmol) in 50 ml THF. After stirring for 0.5h the corresponding (2,2-diethoxyvinyl)triphenylphosphonium tetrafluoroborate 6 or 12 is added. The mixture is stirred for 1.5h at room temperature and refluxed for 3h (work-up: details see procedure A). Bulb-to-bulb distillation (50-100°C/0.05 Torr) yields the orthoesters 15 as colourless, air-sensitive liquids. (Data see table 1).

General Procedure for the Synthesis of 5-Alkylidene-2(5H)-furanones 10 and 2(5H)-Furanones 16:

A solution of 10 mmol of the corresponding orthoester 9 or 15 in 25 ml of dichloromethane is stirred with 20 ml of 1% aqueous p-toluenesulphonic acid for 2h. The organic phase is dried with sodium sulphate. Bulb-to-bulb distillation gives lactones 10 or 16 as colourless liquids. (Data see table 1).

General Procedure for the Synthesis of 2-Ethoxyfurans 17:

A solution of 10 mmol of the corresponding orthoester 15 in 25 ml of dichloromethane is stirred vigorously with 1 ml of water for 24h. The organic phase is dried with sodium sulphate. Bulb-to-bulb distillation gives 2-ethoxyfurans 17 as colourless, air-sensitive liquids. (Data see table 1).

Table 1: Compounds prepared 9, 10, 15, 16, and 17

Product	Yield [%]	b.p.[°C]/Torr m.p.[°C] (Solvent)	MS m/z (M^+)	IR (KBr/100%) [cm^{-1}]	^{1}H-NMR ($CDCl_3$/TMS) [ppm]	^{13}C-NMR ($CDCl_3$/TMS) [ppm]
9a	71	53 (MeOH)	322	1640 (C=C).	1.26 (t, 6H, CH_3); 3.73 (t, 4H, OCH_2); 5.56 (s, 1H, =CH_2); 6.03 (s, 1H, =CH); 7.26 (m, 2H, CH); 7.43 (s, 6H, CH); 7.66 (m, 2H, CH).	15.28 (CH_3); 59.45 (OCH_2); 102.65 (Cq); 124.49, 124.73, 126.43, 128.54, 128.55 (arom. C); 131.86, 135.32, 144.30, 153.30, 153.30 (=C).
9b	69	80/0.5	274	1665 (C=C).	1.28 (t, 6H, CH_2); 1.43 (s, 3H, CH_3); 1.89 (s, 3H, CH_3); 3.73 (q, 4H, OCH_2); 5.83 (s, 1H, =CH); 7.40 (s, 5H, CH).	15.38, 18.44, 19.41 (CH_3); 58.75 (OCH_2); 108.93 (Cq); 121.40, 135.01, 143.12, 143.73 (=C); 126.25, 128.10, 128.34, 129.01 (arom. C).
10a	83	114 (MeOH)	248	1760 (C=O).	6.15 (s, 2H, =CH); 7.36 (m, 2H, CH); 7.50 (s, 6H, CH); 7.76 (m, 2H, CH).	113.63, 114.30 (=CH); 128.28, 128.58, 129.07, 130.32, 130.59, 132.77 (arom. C); 147.59, 158.58 (=C); 168.51 (C=O).
10b	82	86 (Ether)	200	1755 (C=C).	1.60 (s, 3H, CH_3); 2.10 (s, 3H, CH_3); 6.03 (s, 1H, =CH); 7.40 (s, 5H, CH).	19.22, 20.55 (CH_3); 117.80 (=CH); 152.64, 127.55, 128.29, 129.08 (arom. C); 132.86, 144.31, 156.71 (=C); 168.08 (C=O).
15a	76	76/0.01	284	1744 (C=O).	1.17 (t, 6H, CH_3); 1.37-2.09 (m, 8H, CH_2); 3.06 (s, 2H, CH_2); 3.43, 3.56 (q, 2H, OCH_2); 3.70 (s, 3H, OCH_3); 4.30 (m, 1H, CH).	14.92 (CH_3); 22.72, 25.05, 25.84, 28.63, 34.09 (CH_2); 51.50 (OCH_3); 53.51, 58.24, (OCH_2); 81.60 (CH); 118.51, 144.88 (=C); 125.31 (Cq); 170.56 (C=O).
15b	67	60/0.01	196 (M-46)	1640 (C=C).	1.20 (t, 6H, CH_3); 1.30 (d, 3H, CH_3); 1.70 (s, 3H, CH_3); 2.80 (d, 2H, CH_2); 3.35 (q, 2H, OCH_2); 3.50 (q, 2H, OCH_2); 4.55 (q, 1H, CH); 5.05 (m, 2H, =CH_2); 5.80 (m, 1H, =CH).	9.86, 14.89, 19.08 (CH_3); 28.45 (CH_2); 57.46, 58.12 (OCH_2); 80.48 (CH); 115.12 (=CH_2); 125.47, 126.95 (=C); 134.77 (=CH); 139.84 (Cq).
15c	83	70/0.8	240	1675 (C=C).	1.3 (t, 6H, CH_3); 1.58 (m, 10H, CH_2); 1.73 (d, 3H, CH_3); 3.59 (q, 4H, OCH_2); 5.36 (d, 1H, =CH).	11.61, 15.13 (CH_3); 21.87, 24.90, 33.91 (CH_2); 57.78 (OCH_2); 87.45 (Spiro-C); 119.21 (=CH); 122.49 (Cq); 149.85 (=C).

Table 1: Continued

Product	Yield [%]	b.p.[°C]/Torr m.p.[°C] (Solvent)	MS m/z (M^+)	IR (KBr/100%) [cm^{-1}]	^{1}H-NMR ($CDCl_3$/TMS) [ppm]	^{13}C-NMR ($CDCl_3$/TMS) [ppm]
15d	83	56/0.01	239 (M-15)	1655 (C=C).	1.13 (s, 3H, CH_3); 1.22 (t, 6H, CH_3); 1.50 (s, 3H, CH_3); 1.40-2.33 (m, 6H, CH_2); 3.52, 3.70 (q, 2H, OCH_2); 5.35 (s, 1H, =CH).	15.07, 15.25 (CH_3); 19.83, 24.75, 25.99 (CH_2); 30.0 (CH_3); 34.43 (Cq); 40.13, 41.25 (CH_3); 57.21, 58.33 (OCH_2); 85.81 (Cq); 116.03 (=C); 121.91 (Cq); 159.55 (=C).
16a	81	51 (Ether)	210	1730, 1745 (C=O).	0.9-3.07 (m, 8H, CH_2); 3.30 (s, 2H, CH_2); 3.70 (s, 3H, OCH_3); 4.75 (t, 1H, CH).	22.23, 25.87, 26.36, 27.99, 33.97 (CH_2); 51.84 (OCH_3); 80.08 (CH); 116.48 (=CH); 166.29 (=C); 169.59 (C=O); 173.03 (C=O).
16b	70	55/0.01	152	1640 (C=C); 1740 (C=O).	1.45 (d, 3H, CH_3); 2.05 (s, 3H, CH_3); 3.00 (d, 2H, CH_2); 4.90 (q, 1H, CH); 5.05 (d, 2H, $=CH_2$); 5.90 (m, 1H, =CH).	11.59, 18.05 (CH_3); 27.36 (CH_2); 79.30 (CH); 115.82, 124.38 (=C); 133.26 (=CH); 161.83 (=C); 173.42 (C=O).
16c	92	51 (Ether)	166	1634 (C=C), 1735 (C=O).	1.4-1.97 (m, 10H, CH_2); 2.03 (d, 3H, 5.70 (m, 1H, =CH).	12.61 (CH_3); 21.35, 23.93, 32.70 (CH_2); 88.36 (Spiro-C); 114.81 (=CH); 171.78 (=C); 173.03 (C=O).
16d	87	63/0.01	180	1625 (C=C); 1745 (C=O).	1.23, 1.28, 1.55 (s, 3H, CH_3); 1.62-2.44 (m, 6H, CH_2); 5.61 (s, 1H, =CH).	19.02, 23.57, 23.78 (CH2); 29.21, 39.52, 41.01 (CH_3); 35.88 (Cq); 86.51 (C-O); 111.6 (=CH); 171.09 (=C); 181.88 (C=O).
17a	75	75/0.15	238	1620 (C=C), 1740 (C=O).	1.37 (t, 3H, CH_3); 1.58-2.10, 2.10-2.81 (m, 4H, CH_2); 4.03 (q, 2H, OCH_2); 4.97 (s, 1H, =CH).	14.44 (CH_3); 22.11, 22.34, 22.93 (CH_2); 66.52 (OCH_2); 81.08 (=CH); 117.18, 140.02, 159.07 (=C).
17b	66	45/0.01	180	1615, 1660 (C=C).	1.30 (t, 3H, CH_3); 1.80 (s, 3H, CH_3); 2.10 (s, 3H, CH_3); 2.95 (d, 2H, CH_2); 4.05 (q, 2H, OCH_2); 5.00 (d, 2H, $=CH_2$); 5.85 (m, 1H, =CH).	8.52, 10.98, 15.08 (CH_3); 26.70 (CH_2); 69.01 (OCH_2); 98.77, 114.90, 137.20, 153.59 (=C); 114.30 ($=CH_2$); 136.81 (=CH).

Table 2: Analytical Data of Compounds 9, 10, 15, 16 and 17

Compound	Formula	Found [%]	Calc. [%]
9a	$C_{21}H_{22}O_3$ (322.4)	C 77.97 H 6.85	C 78.23 H 6.87
9b	$C_{17}H_{22}O_3$ (274.4)	C 74.28 H 8.12	C 74.42 H 8.08
10a	$C_{17}H_{12}O_2$ (248.3)	C 81.79 H 4.57	C 82.24 H 4.86
10b	$C_{13}H_{12}O_2$ (200.2)	C 77.09 H 6.01	C 78.07 H 6.03
15a	$C_{15}H_{24}O_5$ (284.3)	C 62.85 H 8.46	C 63.36 H 8.50
15b	$C_{13}H_{22}O_5$ (258.3)	C 60.05 H 8.42	C 60.45 H 8.58
15c	$C_{14}H_{24}O_3$ (240.3)	C 69.50 H 10.11	C 69.69 H 10.06
15d	$C_{15}H_{26}O_3$ (254.4)	C 70.46 H 10.29	C 70.80 H 10.30
16a	$C_{11}H_{14}O_4$ (210.0)	C 62.56 H 6.63	C 62.84 H 6.71
16b	$C_9H_{12}O_2$ (152.2)	C 70.64 H 7.96	C 71.03 H 7.95
16c	$C_{10}H_{14}O_2$ (166.2)	C 71.96 H 8.87	C 72.25 H 8.84
16d	$C_{11}H_{16}O_2$ (180.2)	C 73.05 H 8.79	C 73.30 H 8.94
17a	$C_{10}H_{14}O_4$ (198.2)	C 60.12 H 7.03	C 60.59 H 7.11
17b	$C_{11}H_{16}O_2$ (180.3)	C 73.03 H 8.87	C 73.30 H 8.95

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Correspondent

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