Reactions of 2,5-Furandicarbaldehyde with Stabilized Phosphonium Ylides. Applications to the Synthesis of 5-Vinyl-2-furaldehyde and 2,5-Divinylfuran Derivatives

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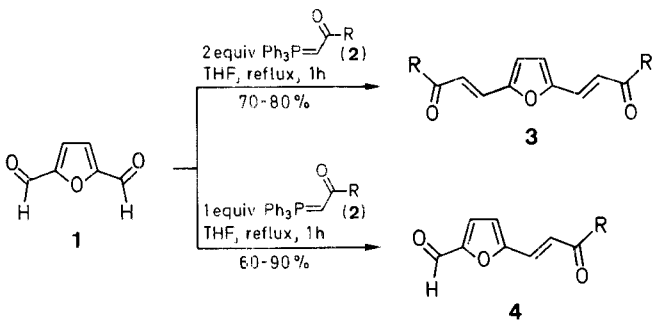
By simple modification of the molar proportion of reactants, it was possible to selectively functionalize an aldehyde group in 2,5-furandicarbaldehyde (**1**), by Wittig reaction with stabilized ylides **2**. The scope of the procedure is extended to the preparation of certain furan-containing natural fatty acid analogues.

2,5-Furandicarbaldehyde (**1**) is an important synthetic intermediate for the preparation of interesting compounds starting from hexoses,[1] and it has already attracted the attention of a number of researchers,[2,3] especially for the preparation of furan containing macrocycles.[4] Nevertheless, the conversion of this compound to systems such as 2,5-bisethylidene derivatives **3**, by a Wittig reaction[5] with stabilized ylides **2**, has been relatively unexplored.[6] The conversion of **1** into 2-formyl-5-ethylidene derivatives **4**[7] has been even less studied. In this paper, the syntheses of the symmetric **3**, and asymmetric derivatives **4** and **6** of 2,5-furandicarbaldehyde (**1**) by Wittig condensation with stabilized ylides are reported.

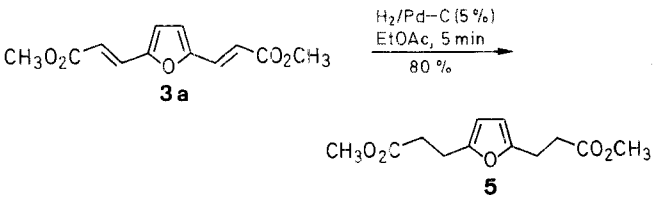


2–4	R
a	OCH_3
b	CH_3
c	Ph

Scheme **A**

The reaction of **1** with two equivalents of the phosphonium ylide **2** in refluxing tetrahydrofuran gave the furan derivatives **3a–c** in good yields (Scheme **A**). It is worth mentioning that, although the synthesis of **3a** is also possible by a modification of the Horner–Wittig method,[6] and that of **3c** by the aldol condensation of **1** with acetophenone,[2] the synthesis of **3b** is not possible by any of the cited methods.[2,3] All the products **3** were obtained as *E*-stereoisomers (without showing even trace amounts of the corresponding *Z*-isomers), as evidenced by inspection of the coupling constants for the vinylic protons in the range of 16 Hz.[9] (Table 1).

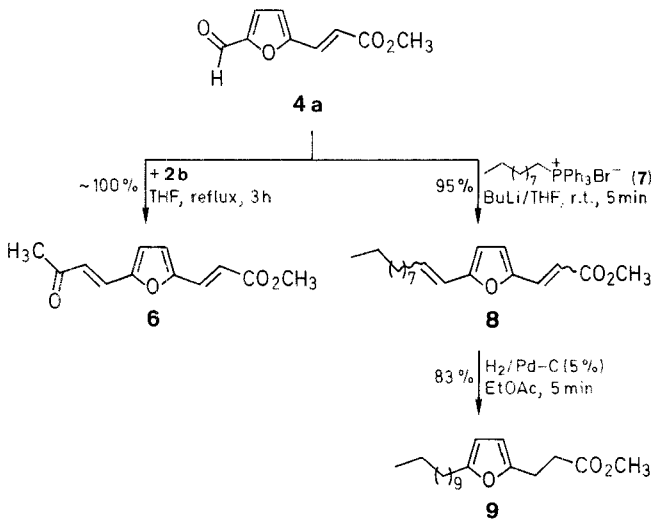
Compound **3a** is an interesting starting material for the synthesis of dimethyl 2,5-furandipropionate (**5**) by hydrogenation of the vinylic double bond in **3a** (Scheme **B**). The corresponding acid is present as a minor component in human urine.[10]



Scheme **B**

Alternatively, the reaction of **1** with one equivalent of the corresponding phosphonium ylide **2**, under the same conditions mentioned above gave the aldehydes **4a–c** as *E*-stereoisomers in very good overall yields (Scheme **A**) (Table 2). The product **4a** has been previously obtained in substantially lower yields from 5-hydroxymethyl-2-furaldehyde[11] and 2-furaldehyde[12] as starting materials.

On the other hand, the reaction of ester **4a** with 2-oxopropylidenetriphenylphosphorane (**2b**) afforded the compound **6** in excellent yield.



Scheme C

Another interesting application of these derivatives, in the field of natural products, is the preparation of furanoid fatty acids. The reaction of **4a** with decyltriphenylphosphonium bromide (**7**) using *n*-butyllithium as the base gave in high yield, product **8** as a not evaluated mixture of *E*/*Z*-stereoisomers. The catalytic hydrogenation of the vinylic double bonds led to the methyl ester **9**, a structural analogue to the fatty acids found in fish oils by Glass[13,14] and Gunstone[15] (Scheme **C**). The synthesis of **9** has been described earlier involving seven steps and in very low overall yield.[16]

In summary, the symmetric or asymmetric functionalization processes of 2,5-furandicarbaldehyde (**1**) via a Wittig reaction is possible by simple modification of the relative proportion of reactants in the reaction conditions described.

The progress of the reaction was monitored by TLC using aluminum coated silica gel plates 60 (Merck), grade II–III in the Brockmann scale. 2,5-Furandicarbaldehyde (**1**) was prepared following a previously described procedure.[1] Phosphonium ylides **2** were synthesized from the corresponding phosphonium salts, obtained by treatment of the corresponding halides with triphenylphosphine.[17] Melting points were taken in capillary tubes using a Büchi 510 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian T-60A spectrometer at 60 MHz. ^{13}C-NMR spectra were obtained using a Varian FT-80A spectrometer. Mass spectra were recorded on a MAT-711 spectrometer at 70 eV.

Table 1. Compounds **3a–c** Prepared

Product	Yield[a] (%)	mp (°C) (EtOH)	Molecular Formula[b] or Lit. mp (°C)	IR (KBr) ν(cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS) δ, J(Hz)	^{13}C-NMR (CDCl$_3$/TMS) δ	MS *m/z* (%)
3a	80	138–140	$C_{12}H_{12}O_5$ (236.2)	1725	3.7 (s, 6H, OCH_3); 6.6 (s, 2H$_{Furyl}$); 6.4, 7.4 (ABq, 4H, $CH_B=CH_ACO_2CH_3$, $J_{AB}=16$)	51.53 (OCH_3); 116.53 ($CH=\underline{C}HCO_2CH_3$); 117.30 (C-3$_{Furyl}$); 129.98 ($\underline{C}H=CHCO_2CH_3$); 152.19 (C-2$_{Furyl}$); 166.74 ($\underline{C}O_2CH_3$)	236 (M^+, 100); 205 ($M^+ - OCH_3$, 80)
3b	73	127–128	$C_{12}H_{12}O_3$ (204.2)	1700	2.3 (s, 6H, CH_3CO); 6.7 (s, 2H$_{Furyl}$); 6.7–7.3 (ABq, 4H, $CH_B=CH_ACOCH_3$, $J_{AB}=16$)	27.54 ($\underline{C}H_3CO$); 117.36 (C-3$_{Furyl}$); 125.54 ($CH=\underline{C}HCOCH_3$); 127.81 ($\underline{C}H=CHCOCH_3$); 152.26 (C-2$_{Furyl}$); 196.85 (C=O)	205 ($M^+ + 1$, 100); 204 (M^+, 17)
3c	70	160–162	163.5–164[2]	1660	6.7 (s, 2H$_{Furyl}$); 7.4–7.6 (m, 10H, H$_{arom+olefin}$); 7.8–8.2 (m, 4H$_{arom}$)	–	–

[a] Yield of isolated product based on **1**.

[b] Satisfactory microanalyses obtained: C ±0.23, H ±0.08.

Table 2. Compounds **4a–c** Prepared

Product	Yield[a] (%)	mp (°C) (EtOH)	Molecular Formula[b] or Lit. mp (°C)	IR (KBr) ν(cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS) δ, J(Hz)	^{13}C-NMR (CDCl$_3$/TMS) δ
4a[c]	70	102–103	106–106.5[9] 106–107[10]	1710, 1670	3.8 (s, 3H, OCH_3); 6.8–7.3 (ABq, 2H$_{Furyl}$, $J=4$); 6.6, 7.5 (ABq, 2H, $CH_B=CH_ACO_2CH_3$, $J_{AB}=16$); 9.7 (s, 1H, CHO)	78.46 (OCH_3); 120.69 (C-3, het); 121.73 (C-4$_{Furyl}$); 115.35 ($CH=\underline{C}HCO_2CH_3$); 129.63 ($\underline{C}H=CHCO_2CH_3$); 152.76 (C-5, het); 154.75 (C-2$_{Furyl}$); 166.13 ($\underline{C}O_2CH_3$); 177.52 (CHO)
4b	60	110–111	$C_9H_8O_3$ (164.2)	1710	2.4 (s, 3H, CH_3CO); 6.8–7.3 (ABq, 2H$_{Furyl}$, $J=4$); 6.9–7.3 (ABq, 2H, $CH_B=CH_ACOCH_3$, $J_{AB}=16$); 9.7 (s, 1H, CHO)	27.87 ($\underline{C}H_3CO$); 115.87 (C-3$_{Furyl}$); 122.10 (C-4$_{Furyl}$); 127.42 ($CH=\underline{C}HCOCH_3$); 128.19 ($\underline{C}H=CHCOCH_3$); 152.58 (C-5$_{Furyl}$); 154.81 (C-2$_{Furyl}$); 177.38 ($\underline{C}OCH_3$); 196.66 (CHO)
4c	90	90–92	$C_{14}H_{10}O_3$ (226.2)	1685, 1675	6.8–7.2 (ABq, 2H$_{Furyl}$, $J=4$); 7.2–8.1 (m, 7H$_{arom+olefin}$); 9.3 (s, 1H, CHO)	–

[a] Yield of isolated product based on **1**.

[b] Satisfactory microanalyses obtained: C ±0.23, H ±0.09.

[c] MS: m/z = 180 (M^+, 58); 151 ($M^+ - CHO$, 100); 149 ($M^+ - OCH_3$, 77).

Wittig Reactions of 2,5-Furandicarbaldehyde (1) with Stabilized Phosphonium Ylides 2. Symmetric Derivatives 3a–c; General Procedure:
In a 100 mL round-bottomed flask fitted with a stirrer and reflux condenser, 2,5-furandicarbaldehyde (**1**; 300 mg, 2.42 mmol) is dissolved in THF (40 mL), and the corresponding ylide **2** (4.84 mmol) is added. The solution is stirred at reflux for 1 h, and then the solvent is evaporated at reduced pressure. The crude product **3** is chromatographed on a silica gel column (50 × 5 cm) using a mixture EtOAc/*n*-hexane (1:1) (Table 1).

Dimethyl 2,5-Furandipropionate (5):
A solution of **3a** (100 mg, 0.42 mmol) in EtOAc (10 mL) is hydrogenated in the presence of 5% Pd/C (50 mg) as catalyst for 5 minutes at atmospheric pressure. The mixture is filtered, the solvent is removed, and the product is purified by vacuum distillation; yield: 80 mg (80%); bp 105°C/0.2 mbar (Kugelrohr distillation).

$C_{12}H_{16}O_5$ (240.3) calc. C 59.99 H 6.71 found 60.23 6.81

IR (film): $\nu = 1720\ cm^{-1}$.

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.5–3.0 (m, 8 H, 2 × CH_2CH_2); 3.7 (s, 6 H, 2 × OCH_3); 5.9 (s, 2 H_{Furyl}).

^{13}C-NMR ($CDCl_3$): δ = 22.93 ($\underline{C}H_2CH_2CO_2CH_3$); 31.92 ($\underline{C}H_2CO_2CH_3$); 51.24 ($O\underline{C}H_3$); 101.31 (C-3$_{Furyl}$); 152.23 (C-2$_{Furyl}$); 172.39 ($\underline{C}O_2CH_2$).

Wittig Reactions of 2,5-Furandicarbaldehyde (1) with Stabilized Phosphonium Ylides 2. Asymmetric Derivatives 4a–c; General Procedure:
In a 100 mL round-bottomed flask fitted with a stirrer and reflux condenser, 2,5-furandicarbaldehyde (**1**; 300 mg, 2.42 mmol) is dissolved in THF (30 mL), and the corresponding ylide **2** (2.42 mmol) is added. The solution is stirred at reflux for 1 h, and then the solvent is evaporated at reduced pressure. The crude product **4** is chromatographed on a silica gel column (50 × 5 cm) using a mixture EtOAc/*n*-hexane (1:1) (Table 2).

(*E,E*)-2-(2-Methoxycarbonylvinyl)-5-(3-oxo-1-butenyl)furan (6):
In a 50 mL round-bottomed flask fitted with a stirrer and reflux condenser, 5-(2-methoxycarbonylvinyl)-2-furaldehyde (**4a**; 200 mg, 1.1 mmol) is dissolved in THF (30 mL), and 3-oxopropylidenetriphenylphosphorane (**2b**; 350 mg, 1.1 mmol) is added. The solution is stirred at reflux for 3 h, and then the solvent is evaporated at reduced pressure. The crude product is chromatographed on a silica gel column (50 × 5 cm) using a mixture EtOAc/*n*-hexane (1:1); yield: 242 mg (~100%); mp 110–111°C (EtOH/*n*-hexane, 1.5:1).

$C_{12}H_{12}O_4$ (220.2) calc. C 65.46 H 5.49 found 65.51 5.46

IR (KBr): ν = 1730 (ester C=O), 1660 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.2 (s, 3 H, CH_3CO); 3.7 (s, 3 H, OCH_3); 6.4, 6.6 (ABq, 2 H_{Furyl}); 6.3, 7.2 (ABq, 2 H, $CH_B = CH_ACO_2CH_3$, J_{AB} = 16 Hz); 6.6, 7.1 (AB$_q$, 2 H, $CH_B = CH_ACOCH_3$, J_{AB} = 16 Hz).

^{13}C-NMR ($CDCl_3$): δ = 27.58 ($\underline{C}H_3CO$); 51.33 (OCH_3); 116.59 (CH=$\underline{C}$HCO$_2$CH$_3$); 117.19 (C-3$_{Furyl}$); 117.23 (C-4$_{Furyl}$); 127.86 (CH=$\underline{C}$HCOCH$_3$); 125.45 (CH=$\underline{C}$HCOCH$_3$); 129.73 ($\underline{C}$H=CHCO$_2$CH$_3$); 152.15 (C-2, C-5$_{Furyl}$); 166.44 ($\underline{C}O_2CH_3$); 196.85 ($\underline{C}OCH_3$).

MS (70 eV): m/z = 220 (M^+, 100); 205 ($M^+ - CH_3$, 67); 189 ($M^+ - OCH_3$); 171 ($M^+ - CO_2CH_3$, 16).

(*E/Z*)-2-(2-Methoxycarbonylvinyl)-5-(1-undecenyl)furan (8):
Decyltriphenylphosphonium Bromide (**7**): In a round-bottomed flask fitted with a stirrer, addition funnel and reflux condenser, 1-decyl bromide (1.69 g, 7.63 mmol) is dissolved in dry benzene (1 mL). The mixture is heated to reflux and then a solution of triphenylphosphine (2 g, 7.63 mmol) in dry benzene (2 mL) is added. The mixture is kept at reflux for 6 h, and the solvent is evaporated at reduced pressure. The crude product is washed with ether (2 × 5 mL), and the resulting oil is dried at 50°C/0.13 mbar. The resulting oil is identified by its IR spectrum and microanalytical data as decyltriphenylphosphonium bromide (**7**).

$C_{12}H_{12}O_4$ (403.6) calc. C 83.33 H 8.99 found 83.42 8.86

IR (CCl_4): ν = 3000–2820, 2000–1800, 1730, 1590, 1440, 1100 cm^{-1}.

Preparation of **8** *from* **4a** *and* **7**: In a three-necked, argon-filled round-bottomed flask fitted with a stirrer and septum, decyltriphenylphosphonium bromide (**7**; 960 mg, 7.63 mmol) is suspended in dry THF (40 mL). A 1.6 M solution of BuLi in hexane (2.47 mL, 3.96 mmol) is added dropwise with a syringe, and the stirring is continued at room temperature for 30 min (until the solid is dissolved). To the above solution, a solution of **4a** (238 mg, 1.32 mmol) in dry THF (20 mL) is added dropwise with a syringe, and stirring is continued at room temperature for 5 min. The mixture is quenched with brine (50 mL), the organic layer is separated, and the aqueous layer is extracted with ether (2 × 25 mL). The organic extracts are combined and dried ($MgSO_4$). The solvent is evaporated at reduced pressure to afford a yellow solid, which is chromatographed on a silica gel column (40 × 3 cm) using a mixture EtOAc/*n*-hexane (1:1), giving a pale yellow oil; yield: 400 mg (95%).

$C_{19}H_{28}O_3$ (304.4) calc. C 74.96 H 9.27 found 75.21 9.16

IR (KBr): ν = 1715 (C=O); 1630, 1640 cm^{-1} (C=C).

^{1}H-NMR ($CDCl_3$/TMS):[18] δ = 0.9–1.6 (m, 17 H, H-11 to H-18); 2.1–2.7 (m, 2 H, H-10); 3.7 (s, 3 H, OCH_3); 5.4–6.3 (m, 4 H, H-2, H-6, H-8, 9); 6.5 (d, 1 H, H-5, $J_{5,6}$ = 4 Hz); 7.2 (d, 1 H, H-3, J = 15 Hz).

^{13}C-NMR ($CDCl_3$):[18] δ = 13.76 (C-18); 22.40 (C-17); 29.06, 29.10, 29.31 (C-10 to C-15); 31.64 (C-16); 51.08 ($O\underline{C}H_3$); 111.34 (C-9); 114.21 (C-2); 116.48, 115.42 (C-5, C-6); 130.54 (C-3); 134.30 (C-8); 149.34 (C-7); 155.39 (C-4); 167.07 (C-1).

2-(3-Methoxycarbonylpropyl)-5-undecylfuran (9):
Hydrogenation of **8** (130 mg, 0.43 mmol) in EtOAc (13 mL) is carried out in the presence of 5% Pd/C (65 mg) as catalyst for 5 min at atmospheric pressure as described for the preparation of **5**. The mixture is filtered, the solvent removed and the product is purified by vacuum distillation; yield: 110 mg (83%); bp 130°C/0.13 mbar (Kugelrohr distillation).

$C_{19}H_{32}O_3$ (308.5) calc. C 73.98 H 10.45 found 74.18 10.56

IR (CCl_4): ν = 1740 cm^{-1} (C=O).

^{1}H-NMR ($CDCl_3$/TMS):[18,19] δ = 0.8–1.6 (m, 21 H, H-18 to H-9); 2.4–3.0 (m, 6 H, H-2, H-3, H-8); 3.6 (s, 3 H, OCH_3); 5.7 (br s, 2 H_{Furyl}).

^{13}C-NMR ($CDCl_3$):[18,19] δ = 13.88 (C-18); 22.48 (C-17); 23.37 (C-3); 27.83 (C-9, C-8); 29.00, 29.16, 29.43 (C-10 to C-15); 31.71 (C-16); 32.45 (C-2); 51.39 ($O\underline{C}H_3$); 104.79 (C-6); 105.38 (C-5); 151.82 (C-4); 155.05 (C-7); 172.84 (C-1).

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