

Expedient Synthesis of 2-Carboethoxy-4-methylnaphthalenes[#]

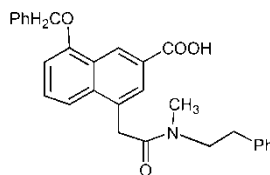
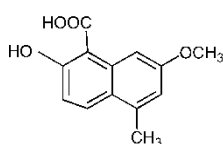
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Abstract: A three-step synthesis of 2-carboethoxy-4-methylnaphthalenes **7a–d** from aryl aldehydes is described.

Keywords: Benzannulations, naphthalene, Wacker reaction, Wittig reaction

The naphthalene structural motif is widely present in nature^[1] and in important biologically active molecules.^[2] For example, **1** is a segment of anticancer agent neocarzinostatin.^[2a] Compound **2** is an orally active leukotriene B₄ receptor antagonist.^[3] Various methods^[3,4] are available for the synthesis of such naphthalene segments. However, most of these methods are either multistep methods or are useful to synthesize a specific segment. In view of this, we envisaged developing a convenient method for the synthesis of substituted 2-carboethoxy-4-methylnaphthalenes, which could act as common precursors for compounds such as **1** and **2** by carrying out normal functional-group transformations.



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[#]Dedicated to Professor S. C. Chandrasekaran on the occasion of his 60th Birthday.

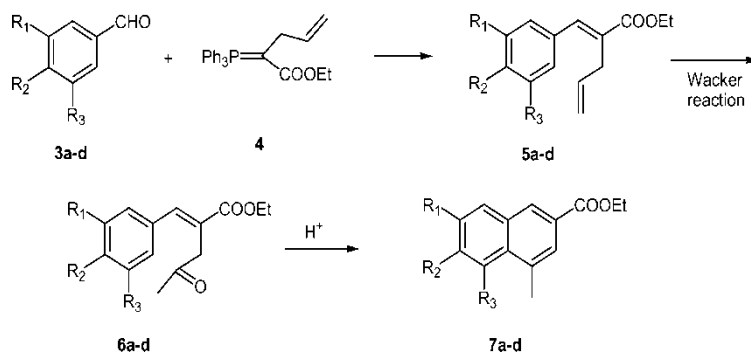
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We had earlier used Pd-C-catalyzed ring annulation of the indole ring to carbazole the precursor of anticancer alkaloid olivacine.^[5] Because we were not able to extend the same method for benzannulations to naphthalene, we thought that if we could convert the terminal olefin (Scheme 1) to a methyl ketone group by the Wacker reaction, we may get the naphthalene by ring annulation. Thus, the pentenoate **5a** obtained by Wittig condensation with phosphorane **4** on Wacker oxidation gave the keto-ester **6a** in 70% yield. The latter compounds are also useful substrates for the synthesis^[6] of substituted γ -lactones. Keto ester **6a** was then cyclized to 2-carboethoxy-4-methyl naphthalene (**7a**) using PPA in good yield. With the facile preparation of naphthalene **7a**, we used this sequence of reactions to synthesize several substituted 2-carboethoxy-4-methylnaphthalenes (**7b–d**). In conclusion, we have developed an efficient three-step method for the synthesis of 2-carboethoxy-4-methylnaphthalenes (Table 1).

All melting points are uncorrected and were measured by the normal thiels-tube (paraffin) method. Column chromatography was performed on silica gel G (13% CaSO₄ as binder). IR spectra were recorded on a Shimadzu FT-IR spectrophotometer (KBr pellet or neat sample). All new compounds gave satisfactorily microanalysis: C \pm 0.50; H \pm 0.30. ¹H NMR and ¹³CMR spectra were recorded on a Bruker 300-MHz instrument. The multiplicities of carbon signals were obtained from Distortionless Enhancement by Polarisation Transfer (DEPT) experiments.

GENERAL PROCEDURE FOR THE PREPARATION OF PENTANOATES 5A–D

A mixture of aryl aldehyde **3a–d** (1 mmol), allyl phosphorane **4** (1 mmol), and chloroform (10 mL) was refluxed for 3 h. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (hexanes–EtOAc = 95 : 5) to yield unsaturated esters **5a–d**.



Scheme 1.

Table 1. Yields of compounds 5, 6, and 7

Compounds 3, 5–7	R_1	R_2	R_3	Compound 5 yield (%)	Compound 6 yield (%)	Compound 7 yield (%)
a	H	H	H	95	75	70
b	MeO	H	H	71	77	69
c	MeO	MeO	H	69	70	71
d	MeO	MeO	MeO	65	72	66

DATA**Ethyl (*E*)-2-Benzylidenepent-4-enoate (5a)^[7]**

Yield: 95%; liquid; bp 136°C. IR (neat): ν_{\max} = 1716, 1635, 1604 cm^{-1} . ¹H NMR (300 MHz, CDCl₃): δ = 1.33 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 3.28 (d, J = 5.4 Hz, 2H, CH₂CH=CH₂), 4.26 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 5.11 (m, 2H, CH₂CH=CH₂), 6.00 (m, 1H, CH₂CH=CH₂), 7.30–7.41 (br.s, 5H, Ar-H), 7.80 (s, 1H, =CH). ¹³C NMR (CDCl₃): δ = 14.18 (OCH₂CH₃), 31.56 (CH₂CH=CH₂), 60.71 (OCH₂CH₃), 115.55 (CH₂CH=CH₂), 128.33 (CH), 128.47 (CH), 128.48 (CH), 129.16 (CH), 130.47 (C), 135.43 (C), 135.60 (CH₂CH=CH₂), 140.04 (CH), 167.83 (CO).

Ethyl (*E*)-2-(*m*-Methoxybenzylidene)pent-4-enoate (5b)

Yield: 71%; oily liquid. IR (neat): 1715, 1635, 1600 cm^{-1} . ¹H NMR (CDCl₃): δ = 1.32 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 3.26 (d, J = 5.4 Hz, 2H, CH₂CH=CH₂), 3.89 (s, 3H, OCH₃), 4.31 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 5.28 (m, 2H, CH₂CH=CH₂), 6.03 (m, 1H, CH₂CH=CH₂), 6.95–7.33 (m, 4H, Ar-H), 7.81 (s, 1H, =CH). ¹³C NMR (CDCl₃): δ = 14.14 (OCH₂CH₃), 31.02 (CH₂CH=CH₂), 57.69 (OCH₃), 61.23 (OCH₂CH₃), 111.67 (CH₂CH=CH₂), 113.12 (CH), 115.32 (CH), 123.03 (C), 128.35 (CH), 128.38 (CH), 135.02 (C), 139.98 (C), 147.74 (CH₂CH=CH₂), 149.11 (CH), 167.55 (CO). GC/MS: m/z = 246 [M]⁺.

Ethyl (*E*)-2-(3,4-Dimethoxybenzylidene)pent-4-enoate (5c)^[7]

Yield: 69%; oily liquid. IR (neat): 1711, 1638, 1606 cm^{-1} . ¹H NMR (CDCl₃): δ = 1.33 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 3.33 (d, J = 5.4 Hz, 2H, CH₂CH=CH₂), 3.87 (s, 3H, OCH₃), 3.90 (s, 3H, OCH₃), 4.27 (q, J = 7.2 Hz, 2H, OCH₂CH₃), 5.13 (m, 2H, CH₂CH=CH₂), 6.03 (m, 1H, CH₂CH=CH₂), 6.88 (d, J = 8.4 Hz, 1H, Ar-H), 7.76 (t, J = 8.4, 1.8 Hz, 2H, Ar-H), 7.76 (s, 1H, =CH). ¹³C NMR (CDCl₃): δ = 14.16 (OCH₂CH₃), 31.65

(CH₂CH=CH₂), 55.87 (OCH₃), 60.53 (OCH₂CH₃), 111.40 (CH₂CH=CH₂), 112.80 (CH), 115.30 (CH), 122.83 (C), 128.35 (C), 128.51 (CH), 135.77 (C), 139.89 (C), 148.94 (CH₂CH=CH₂), 149.81 (CH), 167.95 (CO).

Ethyl (*E*)-2-(3,4,5-Trimethoxybenzylidene)pent-4-enoate (5d)^[7]

Yield: 65%; oily liquid. IR (neat): 1711, 1638, 1585 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.33 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 3.32 (d, *J* = 5.1 Hz, 2H, CH₂CH=CH₂), 3.83 (s, 6H, 2 × OCH₃), 3.86 (s, 3H, OCH₃), 4.26 (q, *J* = 7.2 Hz, 2H, OCH₂CH₃), 5.15 (m, 2H, CH₂CH=CH₂), 6.02 (m, 1H, CH₂CH=CH₂), 6.66 (s, 2H, Ar-H), 7.74 (s, 1H, =CH). ¹³C NMR (CDCl₃): δ = 14.10 (OCH₂CH₃), 37.71 (CH₂CH=CH₂), 55.98 (OCH₃), 60.58 (OCH₂CH₃), 106.68 (CH₂CH=CH₂), 115.30 (CH), 129.44 (C), 130.68 (C), 135.77 (C), 138.65 (C), 140.11 (CH₂CH=CH₂), 152.95 (CH), 167.74 (CO).

GENERAL PROCEDURE FOR THE PREPARATION OF KETO-ESTER 6A–D

A mixture of cuprous chloride (1 mmol), palladium chloride (0.1 mmol), and water (0.2 mL) in DMF (15 mL) was stirred under oxygen atmosphere for 1 h. Ester **5a–d** (1 mmol) in DMF (5 mL) was added, and the mixture was stirred for 10 h at room temperature under an oxygen atmosphere. The reaction mixture was then diluted with water and extracted with EtOAc (3 × 20 mL). The organic layer was dried over anhyd. Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (hexanes 60–80°C–EtOAc = 9 : 1) to yield keto-esters **6a–d**.

DATA

Ethyl-2-benzylidene-4-oxo-pentenoate (6a)^[8]

Yield: 75%; viscous liquid. IR (neat): 1722, 1706 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.25 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 2.17 (s, 3H, CH₂COCH₃), 3.53 (s, 2H, CH₂COCH₃), 4.17 (q, *J* = 7.2 Hz, 2H, OCH₂CH₃), 7.32–7.18 (m, 5H, Ar-H), 7.84 (s, 1H, =CH). ¹³C NMR (CDCl₃): δ = 14.11 (OCH₂CH₃), 29.97 (CH₃CO), 42.43 (CH₂), 61.07 (OCH₂CH₃), 106.13 (CH), 128.49 (CH), 128.68 (CH), 135.10 (C), 141.89 (CH), 153.13 (C), 167.30 (COOEt), 205.94 (CH₃CO).

Ethyl-2-(*m*-methoxybenzylidene)-4-oxo-pentenoate (6b)

Yield: 77%; viscous liquid. IR (neat): 1722, 1700 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.33 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 2.25 (s, 3H, CH₂COCH₃), 3.62

(s, 2H, CH_2COCH_3), 3.80 (s, 3H, OCH_3), 4.26 (q, $J = 7.2$ Hz, 2H, OCH_2CH_3), 6.86–6.90 (m, 2H, Ar-H), 7.26–7.31 (m, 2H, Ar-H), 7.90 (s, 1H, $=\text{CH}$). ^{13}C NMR (CDCl_3): $\delta = 14.20$ (OCH_2CH_3), 29.96 (CH_3CO), 43.33 (CH_2), 54.99 (OCH_3), 61.34 (OCH_2CH_3), 111.46 (CH), 112.40 (CH), 123.23 (CH), 124.80 (C), 127.73 (C), 142.88 (CH), 148.78 (CH), 149.32 (C), 167.63 (COOEt), 205.65 (CH_3CO). GC/MS: $m/z = 262$ $[\text{M}]^+$.

Ethyl-2-(3,4-dimethoxybenzylidene)-4-oxo-pentenoate (6c)

Yield: 70%; viscous liquid. IR (neat): 1722, 1700 cm^{-1} . ^1H NMR (CDCl_3): $\delta = 1.24$ (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 2.17 (s, 3H, CH_2COCH_3), 3.58 (s, 2H, CH_2COCH_3), 3.77 (s, 3H, OCH_3), 4.17 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 6.76–6.84 (m, 3H, Ar-H), 7.84 (s, 1H, $=\text{CH}$). ^{13}C NMR (CDCl_3): $\delta = 14.14$ (OCH_2CH_3), 29.89 (CH_3CO), 42.73 (CH_2), 55.79 (OCH_3), 61.00 (OCH_2CH_3), 110.96 (CH), 112.04 (CH), 122.23 (CH), 124.88 (C), 127.73 (C), 141.98 (CH), 148.78 (CH), 149.72 (C), 167.53 (COOEt), 206.45 (CH_3CO). GC/MS: $m/z = 292$ $[\text{M}]^+$. HRMS: m/z $[\text{M} + \text{Na}^+]$ calcd. for $\text{C}_{16}\text{H}_{20}\text{O}_5$: 315.3207; found: 315.2845.

Ethyl-2-(3,4,5-trimethoxybenzylidene)-4-oxo-pentenoate (6d)

Yield: 72%; viscous liquid. IR (neat): 1722, 1705 cm^{-1} . ^1H NMR (CDCl_3): $\delta = 1.24$ (t, $J = 7.1$ Hz, 3H, OCH_2CH_3), 2.17 (s, 3H, CH_2COCH_3), 3.54 (s, 2H, CH_2COCH_3), 3.73 (s, 6H, $2 \times \text{OCH}_3$), 3.76 (s, 3H, OCH_3), 4.16 (q, $J = 7.1$ Hz, 2H, OCH_2CH_3), 6.49 (s, 2H, Ar-H), 7.76 (s, 1H, $=\text{CH}$). ^{13}C NMR (CDCl_3): $\delta = 14.12$ (OCH_2CH_3), 29.78 (CH_3CO), 42.77 (CH_2), 56.03 (OCH_3), 90.76 (OCH_3), 61.10 (OCH_2CH_3), 106.09 (CH), 126.13 (C), 130.43 (C), 138.64 (C), 142.18 (CH), 153.10 (C), 167.29 (COOEt), 206.40 (CH_3CO). HRMS: m/z $[\text{M} + \text{Na}^+]$ calcd. for $\text{C}_{17}\text{H}_{22}\text{O}_6$: 345.1314; found: 345.1285.

GENERAL PROCEDURE FOR THE PREPARATION NAPHTHALENE 7A–D

A slurry of phosphorus pentoxide (5 g) and 88% phosphoric acid (3 mL) was stirred at 70°C on an oil bath. To this slurry, keto-ester **6a–d** (2 mmol) was added in one portion, and the mixture was stirred for 10 min. After cooling, crushed ice was added, and the reaction mixture was extracted in EtOAc. The organic layer was dried over anhyd. Na_2SO_4 and was concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum ether 60–80°C–EtOAc = 9:1) to yield naphthoic esters **7a–d**.

DATA

Ethyl-4-methyl-2-naphthoate (7a)^[9]

Yield: 70%; white crystals; mp 52°C. IR (KBr): 1722, 1630, 1605 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.46 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 2.73 (s, 3H, ArCH₃), 4.45 (q, *J* = 7.2 Hz, 2H, OCH₂CH₃), 7.52–7.65 (m, 2H, Ar-H), 7.93–8.03 (m, 3H, Ar-H), 8.48 (s, 1H, Ar-H). ¹³C NMR (CDCl₃): δ = 14.35 (OCH₂CH₃), 19.25 (CH₃), 60.94 (OCH₂CH₃), 124.00 (CH), 125.56 (CH), 126.16 (CH), 127.21 (C), 127.95 (CH), 129.35 (CH), 129.94 (CH), 132.61 (C), 134.64 (C), 166.85 (COOEt).

Ethyl-7-methoxy-4-methyl-2-naphthoate (7b)

Yield: 69%; white solid; mp 55°C. IR (KBr): 1710, 1635, 1600 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.44 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 2.69 (s, 3H, ArCH₃), 3.94 (s, 3H, OCH₃), 4.42 (q, *J* = 7.2 Hz, 2H, OCH₂CH₃), 7.26–7.26 (m, 2H, Ar-H), 7.77 (s, 1H, Ar-H), 7.92 (d, *J* = 9.0 Hz, 1H, Ar-H), 8.36 (s, 1H, Ar-H). ¹³C NMR (CDCl₃): δ = 14.30 (OCH₂CH₃), 20.45 (CH₃), 55.67 (OCH₃), 60.78 (OCH₂CH₃), 102.73 (CH), 106.88 (CH), 124.40 (CH), 126.68 (CH), 127.63 (C), 128.73 (CH), 130.22 (C), 133.77 (C), 149.89 (C), 151.52 (C), 168.11 (COOEt). GC/MS: *m/z* = 244 [M]⁺.

Ethyl-6,7-dimethoxy-4-methyl-2-naphthoate (7c)

Yield: 70%; white crystals; mp 144°C. IR (KBr): 1716, 1635, 1601 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.43 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 2.66 (s, 3H, ArCH₃), 4.01 (s, 3H, OCH₃), 4.05 (s, 3H, OCH₃), 4.41 (q, *J* = 7.2 Hz, 2H, OCH₂CH₃), 7.20 (s, 1H, Ar-H), 7.23 (s, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 8.33 (s, 1H, Ar-H). ¹³C NMR (CDCl₃): δ = 14.33 (OCH₂CH₃), 19.47 (CH₃), 55.79 (OCH₃), 60.70 (OCH₂CH₃), 102.73 (CH), 107.98 (CH), 124.42 (CH), 125.62 (C), 127.63 (CH), 128.33 (C), 130.82 (C), 132.78 (C), 149.49 (C), 151.00 (C), 167.05 (COOEt). GC/MS: *m/z* = 274 [M]⁺. HRMS: *m/z* [M + Na⁺] calcd. for C₁₆H₁₈O₄: 297.1103; found: 297.1097.

Ethyl-5,6,7-trimethoxy-4-methyl-2-naphthoate (7d)

Yield: 66%; pale yellow crystals; mp 140°C. IR (KBr): 1720, 1638, 1606 cm⁻¹. ¹H NMR (CDCl₃): δ = 1.43 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 2.88 (s, 3H, ArCH₃), 3.95 (s, 3H, OCH₃), 3.98 (s, 6H, 2 × OCH₃), 4.41 (q, *J* = 7.2 Hz, 2H, OCH₂CH₃), 7.06 (s, 1H, Ar-H), 7.68 (s, 1H, Ar-H),

8.27 (s, 1H, Ar-H). ^{13}C NMR (CDCl_3): $\delta = 14.29$ (OCH_2CH_3), 23.34 (CH_3), 55.67 (OCH_3), 60.79 (OCH_3), 61.15 (OCH_2CH_3), 104.76 (CH), 125.91 (CH), 126.67 (C), 128.01 (CH), 131.13 (C), 134.27 (C), 143.94 (C), 150.46 (C), 152.66 (C), 166.74 (COOEt).

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