A Concise and Efficient Synthesis of (5*R*,7*S*)-Kurzilactone and Its (5*S*,7*R*)-Enantiomer by the Mukaiyama Aldol Reaction

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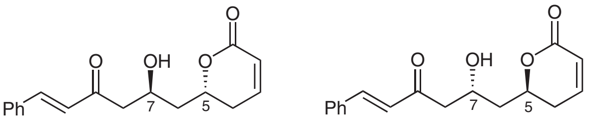
Abstract: Natural kurzilactone (5*R*,7*S*) and its (5*S*,7*R*)-enantiomer were synthesized by a convergent approach using a diastereoselective Mukaiyama aldol reaction to construct the *anti* diol unit. Finally, a ring-closing metathesis reaction led to the target molecule.

Key words: kurzilactone, Mukaiyama reaction, aldol reaction, ring closure, metathesis

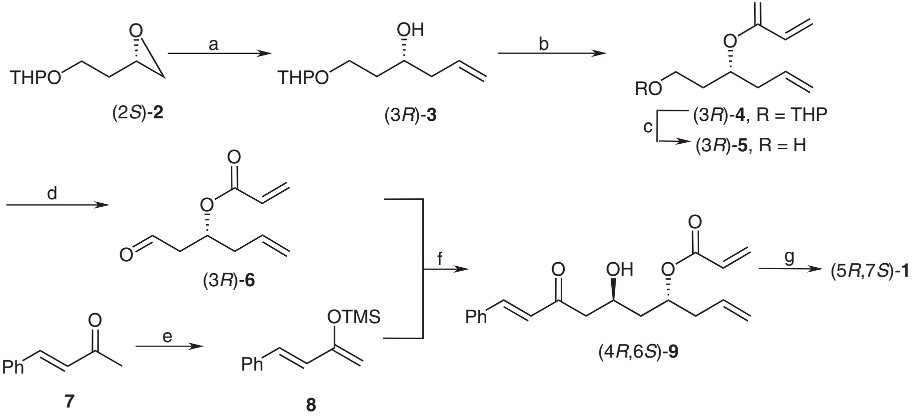
The synthesis of six-membered α,β-unsaturated δ-lactones has generated considerable interest because of their occurrence in large numbers of natural products that possess potent biological activities. Kurzilactone [(5*R*,7*S*)**-1**][1] is one such lactone isolated from the leaves of *Cryptocarya kurzii*, a plant that is indigenous to Malaysia. Kurzilactone exhibits a marked cytotoxicity against the KB human carcinoma cell line (IC$_{50}$ = 1 µg mL^{-1}). Initially, the stereogenic centers bearing hydroxy groups in the side chain were assigned a *syn*-relationship through an NMR experiment, but a corrected *anti*-relationship with a (5*R*,7*S*) configuration of the C(5) and C(7) stereogenic centers was later assigned on the basis of a total synthesis.[2] The structural uniqueness of kurzilactone, coupled with its interesting bioactivity and our interest on the synthesis of 6-substituted α,β-unsaturated δ-lactones,[3] prompted us to explore the synthesis of (5*R*,7*S*)-**1** and its enantiomer (5*S*,7*R*)-**1**. Our strategy involves the stereoselective establishment of the C-7 stereogenic center by means of a Mukaiyama aldol reaction.



(5*R*,7*S*)-**1** (5*S*,7*R*)-**1**

Figure 1 Kurzilactone [(5*R*,7*S*)-**1**] and its enantiomer (5*S*,7*R*)-**1**

We began our synthesis of (5*R*,7*S*)-**1** (Scheme 1) by treating the known epoxide[4] (2*S*)-**2** with vinylmagnesium bromide in the presence of copper(I) cyanide in tetrahydrofuran at –40 °C to give the homoallylic alcohol (3*R*)-**3** in a good yield. Alcohol (3*R*)-**3** was esterified with acryloyl chloride in the presence of *N*,*N*-diisopropylethylamine and a catalytic amount of 4-(dimethylamino)pyridine to give the acryloyl ester (3*R*)-**4** in 75% yield. Removal of the tetrahydropyranyl group, followed by oxidation of the resulting alcohol (3*R*)-**5** with 2-iodobenzoic acid (IBX), gave the aldehyde (3*R*)-**6**. The boron trifluoride diethyl etherate complex mediated Mukaiyama aldol reaction of the aldehyde (3*R*)**-6** with the trimethyl-



Scheme 1 *Reagents and conditions*: (a) H$_2$C=CHMgBr, CuCN, anhyd THF, –40 °C, 90%; (b) DIPEA, acryloyl chloride, DMAP, anhyd CH$_2$Cl$_2$, 0 °C to r.t, 30 min., 75%; (c) PPTS, MeOH, r.t, 12 h, 92%; (d) IBX, DMSO, anhyd CH$_2$Cl$_2$, 0 °C to r.t, 36 h, 95%; (e) Et$_3$N, TMSOTf, anhyd CH$_2$Cl$_2$, –10 °C, 0.5 h, 90%; (f) BF$_3$·OEt$_2$, anhyd CH$_2$Cl$_2$, –78 °C, 1 h, 92%, dr 90:10; (g) Grubbs I catalyst, anhyd CH$_2$Cl$_2$, r.t, 6 h, 95%.

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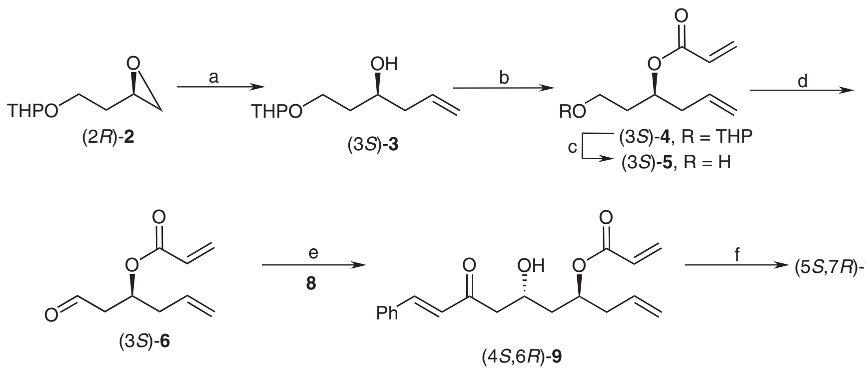

Scheme 2 *Reagents and conditions*: (a) $H_2C{=}CHMgBr$, CuCN, anhyd THF, –40 °C, 90%; (b) DIPEA, acryloyl chloride, DMAP, anhyd CH_2Cl_2, 0 °C to r.t, 30 min., 75%; (c) PPTS, MeOH, r.t, 12 h, 92%; (d) IBX, DMSO, anhyd CH_2Cl_2, 0 °C to r.t, 36 h, 95%; (e) $BF_3{\cdot}OEt_2$, anhyd CH_2Cl_2, –78 °C, 1 h, 85%, dr 90:10; (f) Grubbs I catalyst, anhyd CH_2Cl_2, r.t, 6 h, 89%.

silyl enol ether **8** derived from (3*E*)-4-phenylbut-3-en-2-one (**7**) gave the aldol adduct (4*R*,6*S*)-**9** in 92% yield with good diastereoselectivity (90:10 *anti*:*syn*). Subsequent ring-closing metathesis of the ester in the presence of Grubbs' first-generation catalyst in dichloromethane at room temperature for six hours gave the natural kurzilactone [(5*R*,7*S*)-**1**] in 95% yield. The optical rotation of the synthetic product (5*R*,7*S*)-**1** {$[\alpha]^{25}_D$ +80 (*c* 0.2, $CHCl_3$)} matched the reported value.[2]

The (5*S*,7*R*)-enantiomer of kurzilactone[5] was synthesized in an identical manner, but starting from the known epoxide[4] (2*R*)-**2**, as shown in Scheme 2. The optical rotation {$[\alpha]_D^{25}$ –80 (*c* 0.15 $CHCl_3$)} of the synthetic product (5*S*,7*R*)-**1** was found to be opposite to that reported for natural (5*R*,7*S*)-kurzilactone {$[\alpha]_D^{25}$ +84 (*c* 0.231 $CHCl_3$)}.

In conclusion, we have achieved a short and convergent synthesis of both natural kurzilactone [(5*R*,7*S*)-**1**] and its enantiomer (5*S*,7*R*)-**1**. The highlight of the total synthesis is in the use of the Mukaiyama aldol reaction, which gives the requisite C(7) stereochemistry directly.

Reactions were conducted under N_2 in anhyd solvents such as CH_2Cl_2, THF, and EtOAc. All reactions were monitored by TLC (silica-coated plates, visualization by UV irradiation). Hexane (bp 60–80 °C) was used. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials. Air-sensitive reagents were transferred by syringe or double-ended needle. Solvents were evaporated at reduced pressure on a Buchi rotary evaporator. ^1H and ^{13}C NMR spectra of samples in $CDCl_3$ were recorded on Varian FT-200MHz (Gemini) or Bruker UXNMR FT-300MHz (Avance) spectrometers. The chemical shift δ is reported relative to TMS (δ = 0.0) as an internal standard. Mass spectra were recorded under EI conditions at 70 eV on an LC-MSD (Agilent Technologies) spectrometer. All high-resolution spectra were recorded on a QSTAR XL hybrid MS/MS system (Applied Biosystems/MDS Sciex, Foster City, USA) equipped with an ESI source (IICT, Hyderabad). Column chromatography was performed on silica gel (60–120 mesh) supplied by Acme Chemical Co., India. TLC was performed on Merck 60 F-254 silica gel plates. Optical rotations were measured with a Jasco DIP-370 polarimeter at 20 °C.

(3*R*)-1-(Tetrahydro-2*H*-pyran-2-yloxy)-5-hexen-3-ol [(3*R*)-3]

$Br(CH_2)_2Br$ (2 drops) and freshly prepared $H_2C{=}CHBr$ (1.0 mL, 13.95 mmol) were added sequentially in a dropwise manner to Mg turnings (0.33 g, 13.95 mmol) in anhyd THF (25 mL) at r.t. The mixture was stirred for 0.5 h and then CuCN (10 mg) was added. The mixture was cooled to –78 °C then a soln of epoxide (2*S*)-**2** (1.20 g, 6.97 mmol) in THF (6 mL) was added, and the mixture to warmed to –40 °C and stirred for 4 h. The reaction was quenched with sat. aq NH_4Cl (30 mL) and the mixture was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4; 1 g), and concentrated under reduced pressure. The residue was purified by column chromatography to give (3*R*)-**3** as a yellow liquid; yield: 1.25 g (90%); R_f = 0.3 (PE–EtOAc, 7:3); $[\alpha]_D^{25}$ –3.1 (*c* 1.0, $CHCl_3$).

IR (neat): 3444, 2941, 1439, 1127, 1030 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.86 (m, 1 H), 5.18–5.06 (m, 2 H), 4.61 (m, 1 H, CH), 4.06–3.78 (m, 3 H), 3.69–3.47 (m, 2 H, CH_2), 3.10 (br s, 1 H, OH), 2.27 (t, *J* = 6.9 Hz, 2 H, CH_2), 1.89–1.45 (m, 8 H, 4 × CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.9, 117.3, 98.9, 70.0, 65.9, 62.3, 41.8, 35.7, 30.5, 25.2, 19.4.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{20}O_3Na$: 223.131; found: 223.1313 (ppm error: +1.2798).

(3*S*)-1-(Tetrahydro-2*H*-pyran-2-yloxy)-5-hexen-3-ol [(3*S*)-3]

Compound (3*S*)-**3** was similarly obtained as a liquid from (2*S*)-**2**; yield: 90%; $[\alpha]_D^{25}$ +3.0 (*c* 1.0, $CHCl_3$).

(3*R*)-1-(Tetrahydro-2*H*-pyran-2-yloxy)hex-5-en-3-yl Acrylate [(3*R*)-4]

Acryloyl chloride (0.34 g, 3.75 mmol) was added dropwise under N_2 to a soln of alcohol (3*R*)-**3** (0.75 g, 3.75 mmol), DIPEA (0.70 mL, 5.62 mmol), and DMAP (0.05 mmol) in anhyd CH_2Cl_2 (10 mL). The mixture was stirred at r.t. for 30 min until the reaction was complete (TLC). The mixture was then poured into brine and extracted with CH_2Cl_2 (2 × 20 mL). The organic phases were washed with 1 M aq HCl (5 mL) and brine (8 mL), dried (Na_2SO_4; 1 g), and evaporated under reduced pressure.

The crude product was purified by column chromatography to give (3*R*)-**4** as a liquid; yield: 0.71 g (75%); R_f = 0.5 (PE–EtOAc, 9:1); $[\alpha]_D^{25}$ –15.3 (*c* 1.0, $CHCl_3$).

IR (neat): 2944, 1724, 1406, 1195, 1037 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.39 (td, *J* = 1.1, 17.1 Hz, 1 H), 6.17–6.04 (m, 1 H), 5.86–5.70 (m, 2 H), 5.17 (m, 1 H, CH), 5.14–5.04 (m, 2 H), 4.56 (td, *J* = 3.5, 15.4 Hz, 1 H, CH), 3.89–3.73 (m, 2

H, CH_2), 3.54–3.34 (m, 2 H, CH_2), 2.49–2.32 (m, 2 H, CH_2), 1.97–1.44 (m, 8 H, 4 × CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 133.2, 130.4, 128.6, 117.8, 98.7, 70.9, 63.6, 61.9, 38.7, 33.5, 30.5, 25.3, 19.3.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{14}H_{22}O_4Na$: 277.1415; found: 277.1418 (ppm error: +0.7969).

(3*S*)-1-[2-(Tetrahydro-2 H-2-pyranyloxy)ethyl]-3-butenyl Acrylate [(3*S*)-4]

Compound **(1*S*)-4** was similarly obtained as a liquid from (3*S*)-**3**; yield: 75%; $[\alpha]_D^{25}$ +15.0 (*c* 1.0, $CHCl_3$).

(3*R*)-1-Hydroxyhex-5-en-3-yl Acrylate [(3*R*)-5]

A catalytic amount of PPTS was added to a stirred soln of ester (3*R*)-**4** (0.61 g, 2.4 mmol) in MeOH (20 mL) under N_2, and the mixture was stirred for 12 h at r.t. The reaction was quenched with solid $NaHCO_3$ (1 g), and the mixture was filtered. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography to give compound (3*R*)-**5** as a pale yellow liquid; yield: 0.37 g (92%); R_f = 0.4 (PE–EtOAc, 7:3); $[\alpha]_D^{25}$ –17.0 (*c* = 1, $CHCl_3$).

IR (neat): 3427, 1721, 1407, 1295, 1197, 1052 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.42 (dd, *J* = 1.5, 17.3 Hz, 1 H), 6.16–6.05 (m, 1 H), 5.88–5.68 (m, 2 H), 5.20–5.08 (m, 2 H), 5.06 (m, 1 H), 3.67–3.45 (m, 2 H), 2.47 (br s, 1 H, OH), 2.39 (m, 2 H), 1.94–1.82 (m, 1 H), 1.75–1.63 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 133.1, 131.0, 128.2, 117.8, 70.7, 58.2, 38.7, 36.6.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_9H_{14}O_3Na$: 193.0840; found: 193.0849 (ppm error +4.3287).

(3*S*)-1-Hydroxyhex-5-en-3-yl Acrylate [(3*S*)-5]

Compound (3*S*)-**5** was similarly obtained as a liquid from (3*S*)-**4**; yield: 92%; $[\alpha]_D^{25}$ +17.0 (*c* = 1, $CHCl_3$).

(3*R*)-1-Oxohex-5-en-3-yl Acrylate [(3*R*)-6]

A soln of alcohol (3*R*)-**5** (0.3 g, 1.76 mmol) in anhyd CH_2Cl_2 (8 mL) was added to an ice-cooled soln of 2-iodoxybenzoic acid (0.71 g, 1.65 2.64 mmol) in anhyd DMSO (2.0 mL). The mixture was stirred at r.t. for 12 h then filtered through a pad of Celite that was subsequently washed with Et_2O (10 mL). The combined organic filtrates were washed with H_2O (2 × 5 mL) and brine (5 mL), dried (Na_2SO_4; 1 g), and concentrated in vacuo. The residue was purified by column chromatography to give (3*R*)-**6**; yield: 0.281 g (95%); R_f = 0.5 (PE–EtOAc, 9:1).

IR (neat): 1722, 1407, 1191, 985 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.75 (m, 1 H, CHO), 6.39 (dd, *J* = 1.3, 17.3 Hz, 1 H), 6.09 (dd *J* = 10.3, 17.1 Hz, 1 H), 6.0–5.8 (m, 2 H), 5.25–5.12 (m, 3 H), 3.22 (d, *J* = 6.9 Hz, 2 H, CH_2), 2.83 (t, *J* = 6.4 Hz, 2 H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.3, 165.9, 130.9, 129.9, 128.1, 119.2, 59.2, 47.9, 40.8.

MS (ESI, 70 eV): *m/z* 186 [M + NH_4^+].

(3*S*)-1-Oxohex-5-en-3-yl Acrylate [(3*S*)-6]

Compound (3*S*)-**6** was similarly obtained as a liquid from (3*S*)-**5**; yield: 95%.

(4*R*,6*S*,9*E*)-6-Hydroxy-8-oxo-10-phenyldeca-1,9-dien-4-yl Acrylate [(4*R*,6*S*)-9]

$BF_3·OEt_2$ (0.144 mL, 1.16 mmol) was added dropwise to a soln of the aldehyde (3*R*)-**6** (0.15 g, 0.89 mmol) and silyl enol ether **8** (0.25 g, 1.16 mmol) in anhyd CH_2Cl_2 (10 mL) at –78 °C, and the resulting soln was stirred at –78 °C for 1 h. The reaction was quenched by addition of sat. aq $NaHCO_3$ (3 mL), and the mixture was extracted with $CHCl_3$ (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4; 1 g), filtered, and concentrated. The residue was purified by column chromatography to give (4*R*,6*S*)-**9**; yield: 0.257 g (92%); R_f = 0.3 (PE–EtOAc, 3:2); $[\alpha]_D^{25}$ –15.0 (*c* = 1, $CHCl_3$).

IR (neat): 3478, 1717, 1646, 1609, 1576, 1406, 1273, 1198, 1050 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.48 (m, 3 H), 7.42–7.33 (m, 3 H), 6.68 (dd, *J* = 5.2, 16.6 Hz, 1 H), 6.40 (ddd, *J* = 1.5, 9.0, 17.3 Hz, 1 H), 6.16–6.03 (m, 1 H), 5.86–5.68 (m, 2 H), 5.27–5.03 (m, 3 H), 4.16 (m, 1 H), 3.41 (br s, 1 H, OH), 2.99–2.66 (m, 2 H), 2.52–2.35 (m, 2 H), 1.97–1.66 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.0, 166.0, 143.6, 134.1, 133.2, 131.0, 130.7, 130.6, 128.9, 128.3, 126.2, 118.1, 70.7, 64.6, 46.6, 40.5, 38.9.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{19}H_{22}O_4Na$: 337.1415; found: 337.1405 (ppm error –3.200).

(4*S*,6*R*,9*E*)-6-Hydroxy-8-oxo-10-phenyldeca-1,9-dien-4-yl Acrylate [(4*S*,6*R*)-9]

Compound (4*S*,6*R*)-**9** was similarly obtained as a liquid from (3*S*)-**6**; yield: 85%; $[\alpha]_D^{25}$ +15.8 (*c* = 1, $CHCl_3$).

(6*R*)-6-[(2*S*,5*E*)-2-Hydroxy-4-oxo-6-phenylhex-5-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one [Kurzilactone; (5*R*,7*S*)-1]

Grubbs' first-generation catalyst (0.033 g, 0.0415 mmol) was added to a soln of (4*R*,6*S*)-**9** (0.132 g, 0.415 mmol) in anhyd CH_2Cl_2 (15 ml) at 0 °C, and the mixture was allowed to warm to r.t. over 6 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure and the residue was purified by column chromatography to give (5*R*,7*S*)-**1** as a solid; yield: 0.114 g (95%); mp 74–76 °C; R_f = 0.4 (PE–EtOAc, 1:4); $[\alpha]_D^{25}$ +80 (*c* 0.2, $CHCl_3$).

IR (neat): 3447, 1712, 1652, 1606, 1386, 1253, 1178, 1051 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 16 Hz, 1 H), 7.54–7.39 (m, 5 H), 6.90 (m, 1 H), 6.73 (d, *J* = 16 Hz, 1 H), 6.00 (dd *J* = 2, 10 Hz, 1 H), 4.77 (m, 1 H), 4.5 (m, 1 H), 3.52 (br s, 1 H, OH), 2.93 (dd, *J* = 2.8, 17.4 Hz, 1 H), 2.81 (dd, *J* = 8.8, 17.5 Hz, 1 H), 2.39 (m, 2 H), 1.88 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.4, 164.2, 145.1, 144.0, 134.1, 130.9, 129.0, 128.5, 126.1, 121.5, 75.0, 64.2, 46.9, 41.7, 30.0.

HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{17}H_{18}O_4Na$: 309.1102; found: 309.1094 (ppm error –2.8435).

(6*S*)-6-[(2*R*,5*E*)-2-Hydroxy-4-oxo-6-phenylhex-5-en-1-yl]-5,6-dihydro-2*H*-pyran-2-one [(5*S*,7*R*)-1]

Compound (5*S*,7*R*)-**1** was similarly obtained as a liquid from (4*S*,6*R*)-**9**; yield: 89%; $[\alpha]^{25}_D$ –78 (*c* 0.2, $CHCl_3$).

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