

Highly Concise and Stereoselective Total Synthesis of (5*R*,7*S*)-Kurzilactone

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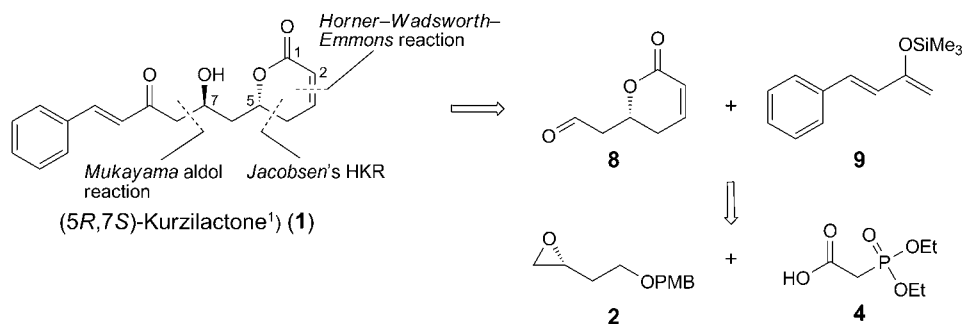
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A highly concise and stereoselective total synthesis of (5*R*,7*S*)-kurzilactone (**1**) was performed by a convergent approach by means of a *Jacobsen's* hydrolytic kinetic resolution, a *Hornner–Wadsworth–Emmons* reaction for the construction of the α,β -unsaturated δ -lactone ring system, and a highly diastereoselective *Mukaiyama* aldol reaction for the introduction of the formal *anti*-1,3-diol unit (*Schemes 2 and 3*).

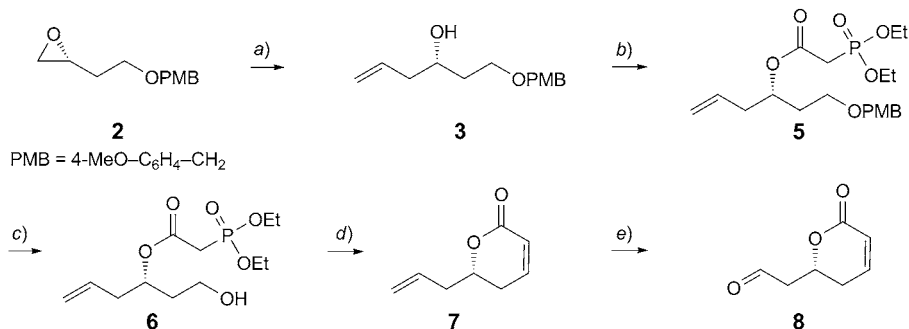
Introduction. – Natural products possessing 6-substituted α,β -unsaturated- δ -lactone moieties have attracted the attention of synthetic organic chemists due to their antitumor properties [1]. In addition, they inhibit HIV proteases [2], induce apoptosis [3][4], and were shown to be antileukemic [5], along with having many other relevant pharmacological properties [6]. (5*R*,7*S*)-Kurzilactone¹⁾ (**1**), an α,β -unsaturated δ -lactone, was isolated from the leaves of *Cryptocarya kurzii*, a plant that is indigenous to Malaysia. Kurzilactone showed a marked cytotoxicity against the KB human-carcinoma cell line ($IC_{50}=1\ \mu\text{g/ml}$) [7]. Initially, the stereogenic centers bearing the OH groups in the side chain and the O-atom of the δ -lactone were assigned a *syn*-relationship through NMR experiment but a corrected *anti*-relationship with (5*R*,7*S*) configuration of the C(5) and C(7) stereogenic centers were later assigned on the basis of a total synthesis [8]. The structural uniqueness of kurzilactone, coupled with its interesting bioactivity and our interest to verify the selectivity of the *Mukaiyama* aldol reaction in case of a δ -lactone-substituted aldehyde instead of an open-chain aldehyde as reported by our group, prompted us to revisit its total synthesis. The retrosynthetic analysis of **1** is described in *Scheme 1*.

Results and Discussion. – Our initial approach to aldehyde **8** employed the oxirane **2** [9] (*Scheme 2*), prepared by *Jacobsen's* hydrolytic kinetic resolution (HKR) [10] of the racemate (*Scheme 2*) in the presence of $[\text{Co}^{\text{III}}\{(\text{R},\text{R})\text{-'salen'}\}(\text{OAc})]$ catalyst ('salen' = *N,N'*-bis[3,5-di(*tert*-butyl)salicylidene]cyclohexane-1,2-diaminato = {[2,2'-(cyclohexane-1,2-diylbis(nitrilomethylidyne)]bis[4,6-di(*tert*-butyl)phenylato]}(2-)). The 4-methoxybenzyl(PMB)-protected (2*R*)-oxirane **2** was obtained as a single enantiomer ($[\alpha]_{\text{D}}^{25} = +10.6$ ($c=1.2$, CHCl_3), ([11]: $[\alpha]_{\text{D}}^{25} = -13.1$ ($c=1.2$, CHCl_3) for the (2*S*)-enantiomer)), which was easily separated from the more polar diol. Oxirane **2** was treated with vinylmagnesium bromide in the presence of CuI to afford

¹⁾ Trivial atom numbering; for the systematic name, see *Exper. Part*.

Scheme 1. Retrosynthetic Analysis of (5*R*,7*S*)-Kurzilactone (**1**)

the homoallyl alcohol **3** in 85% yield. The spectral and analytical data of **3** (ee 94% by HPLC) were in good agreement with the literature values [12]. The C(3) stereogenic center was further confirmed by a modified *Mosher's* method [13]. (3*S*)-Alcohol **3** was esterified with 2-(diethoxyphosphinyl)acetic acid **4** [14] in the presence of dicyclohexylcarbodiimide (DCC) and a catalytic amount of *N,N*-dimethylpyridin-4-amine (DMAP) to afford the (*S*)-ester **5** in 82% yield. Removal of the PMB group with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (=4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile; DDQ) [15] in CH_2Cl_2 yielded hydroxy derivative **6** in 90% yield. Oxidation of **6** with 2-iodoxybenzoic acid (IBX) [16] followed by a *Horner-Wadsworth-Emmons* reaction provided α,β -unsaturated δ -lactone **7** in 68% yield over two steps. The one-step conversion of the terminal olefin moiety of **7** to give aldehyde **8** was achieved by a modified dihydroxylation followed by oxidative cleavage of the diol in 91% yield [17].

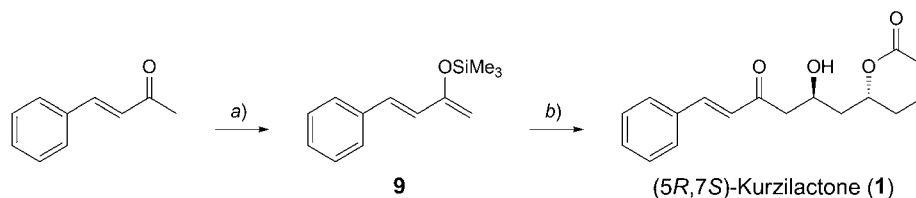
Scheme 2. Synthesis of Aldehyde **8**

a) Vinylmagnesium bromide, CuI THF, 0° to r.t., 2 h; 85%. b) $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{COOH}$ (**4**), DCC, DMAP, CH_2Cl_2 , r.t., 12 h; 62%. c) DDQ, CH_2Cl_2 , H_2O , 0°, 2 h; 90%. d) 1. IBX, DMSO, THF, 0° to r.t., 6 h; 2. NaH, THF, 0°, 2 h; 68% over two steps. e) OsO_4 , 2,6-lutidine (=2,6-dimethylpyridine), NaIO_4 , dioxane, H_2O , r.t., 4 h; 91%.

Having aldehyde **8**, the stage was set to carry out the crucial *Mukaiyama* aldol reaction to verify the selectivity. The $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -mediated *Mukaiyama* aldol reaction of aldehyde **8** with trimethylsilyl enol ether **9** derived from (3*E*)-4-phenylbut-3-en-2-one

afforded the aldol adduct (5*R*,7*S*)-kurzilactone (**1**) as the only product in 95% yield (Scheme 3). It is noteworthy to mention here that in case of the α,β -unsaturated- δ -lactone-substituted aldehyde **8**, the cyclic transition state favored the attack from the opposite face of the lactone center leading to exclusive ($\geq 99\%$) formation of (5*R*,7*S*)-kurzilactone (**1**). The spectral and analytical data of the synthetic (5*R*,7*S*)-kurzilactone (**1**) were in good agreement with the reported value [8].

Scheme 3. Synthesis of (5*R*,7*S*)-Kurzilactone (**1**)



a) Et_3N , $\text{CF}_3\text{SO}_3\text{SiMe}_3$, CH_2Cl_2 , -10° , 30 min. b) **8**, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, CH_2Cl_2 , -78° , 2 h; 81% over two steps.

Conclusions. – We achieved the total synthesis of (5*R*,7*S*)-kurzilactone (**1**) in five longest linear steps starting from a known oxirane by means of a *Horner–Wadsworth–Emmons* reaction for the construction of the α,β -unsaturated δ -lactone ring system and a highly diastereoselective *Mukaiyama* aldol reaction for the introduction of the formal *anti*-1,3-diol unit. Following the same protocol, (5*S*,7*R*)-kurzilactone (*ent*-**1**) could also be synthesized.

Experimental Part

General. Air- and/or moisture-sensitive reactions were carried out in anh. solvents under Ar in an oven- or flame-dried glassware. All anh. solvents were distilled prior to use: THF, benzene, toluene and Et_2O from Na and benzophenone; CH_2Cl_2 , quinoline, and Et_3N from CaH_2 ; MeOH from Mg cake. Commercial reagents were used without purification. Column chromatography (CC): silica gel (SiO_2 , 60–120 mesh). Specific optical rotations: $[\alpha]_D$ in 10^{-1} deg $\text{cm}^2 \text{g}^{-1}$. IR Spectra: in CHCl_3 or neat (as mentioned); $\tilde{\nu}$ in cm^{-1} . ^1H - and ^{13}C -NMR Spectra: at 300 (^1H) and 75 MHz (^{13}C); in CDCl_3 ; δ in ppm rel. to Me_4Si as internal standard, J in Hz.

(3*S*)-1-[4-(4-Methoxyphenyl)methoxy]hex-5-en-3-ol (**3**). To a stirred soln. of **2** (5.0 g, 24.22 mmol) and CuI (0.45 g, 2.40 mmol) in THF (30 ml) was added $\text{CH}_2=\text{CHMgBr}$ (48 ml, 48.02 mmol) at -10° , and stirred at -10° for 1 h. After completion of the reaction (TLC monitoring), it was quenched with sat. NH_4Cl soln. (20 ml). The mixture was extracted with AcOEt (2×60 ml), the combined org. layer washed with H_2O (100 ml) and brine (100 ml), dried (Na_2SO_4), and concentrated, and the residue purified by CC (SiO_2): **3** (4.8 g, 85%). Light yellow liquid. R_f (AcOEt/hexane 3:7) 0.4. $[\alpha]_D^{25} = -6.2$ ($c = 1.1$, CHCl_3) ($[\alpha]_D^{20} = -5.8$ ($c = 1.37$, CHCl_3)). IR (KBr): 2923, 2855, 2380, 1724, 1611, 1512, 1247, 1096, 1034, 822, 560. ^1H -NMR: 7.25 (*d*, $J = 8.4$, 2 H); 6.87 (*d*, $J = 8.4$, 2 H); 5.80–5.72 (*m*, 1 H); 5.14–5.06 (*m*, 2 H); 4.45 (*s*, 2 H); 3.89–3.82 (*m*, 1 H); 3.80 (*s*, 3 H); 3.73–3.57 (*m*, 2 H); 2.27–2.20 (*m*, 2 H); 1.82–1.70 (*m*, 2 H); ^{13}C -NMR: 159.1; 134.8; 129.9; 129.2; 117.4; 113.7; 72.8; 70.3; 68.5; 55.2; 41.8; 35.7. ESI-HR-MS: 259.1305 ($[M + \text{Na}]^+$, $\text{C}_{14}\text{H}_{20}\text{NaO}_3^+$; calc. 259.1306).

(1*S*)-1-[2-[4-(4-Methoxyphenyl)methoxy]ethyl]but-3-en-1-yl 2-(Diethoxyphosphinyl)acetate (**5**). To a stirred soln. of 2-(diethoxyphosphinyl)acetic acid (**4**; 4.5 g, 19.07 mmol) and DCC (7.9 g, 38.14 mmol) in CH_2Cl_2 (50 ml), was added DMAP (1.1 g, 9.05 mmol) at r.t. The mixture was stirred for 15 min before a soln. of **3** (7.4 g, 38 mmol) in CH_2Cl_2 (30 ml) was added at r.t. The mixture was stirred at r.t. for 12 h. After completion of the reaction (TLC monitoring), the mixture was quenched with H_2O (30 ml). The

aq. layer was extracted with CH_2Cl_2 (2×75 ml), the combined org. phase dried (Na_2SO_4), and concentrated, and the residue purified by CC (SiO_2): **5** (4.5 g, 62%). Colorless liquid. R_f (AcOEt/hexane 1:1) 0.3. $[\alpha]_{\text{D}}^{25} = +20.4$ ($c = 1.5$, CHCl_3). IR (KBr): 3328, 2926, 2853, 1666, 1734, 1625, 1250, 1029, 966, 610. $^1\text{H-NMR}$: 7.24 ($d, J = 8.4$, 2 H); 6.86 ($d, J = 8.4$, 2 H); 5.73–5.69 (m , 1 H); 5.17–5.04 (m , 3 H); 4.39 (s , 2 H); 4.20–4.08 (m , 4 H); 3.82–3.76 (s , 3 H); 3.57–3.43 (m , 2 H); 2.92 ($d, J = 21.5$, 2 H); 2.42–2.27 (m , 2 H); 1.91–1.80 (m , 2 H); 1.34 ($dd, J = 6.97, 0.37$, 6 H). $^{13}\text{C-NMR}$: 164.4; 158.3; 132.4; 129.6; 128.5; 117.3; 112.9; 71.8; 71.4; 65.2; 61.7; 54.4; 37.8; 34.4; 33.2; 15.6. ESI-HR-MS: 437.1705 ($[M + \text{Na}]^+$, $\text{C}_{20}\text{H}_{32}\text{NaO}_7\text{P}^+$; calc. 437.1726).

(1*S*)-1-(2-Hydroxyethyl)but-3-en-1-yl 2-(Diethoxyphosphinyl)acetate (**6**). To a stirred soln. of **5** (4.5 g, 10.81 mmol) in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ 9:1 (50 ml) was added DDQ (2.9 g, 13.12 mmol) at 0° , and the mixture was stirred for 2 h. After completion (TLC monitoring), the reaction was quenched with sat. aq. NaHCO_3 soln. (25 ml). The mixture was filtered through *Celite*, the aq. layer extracted with CH_2Cl_2 (2×40 ml), the combined org. phase washed with H_2O (50 ml) and brine (50 ml), dried (Na_2SO_4), and concentrated, and the residue purified by CC (SiO_2): **6** (2.87 g, 90%). Colorless liquid. R_f (AcOEt/hexane 4:1) 0.2. $[\alpha]_{\text{D}}^{25} = +10.6$ ($c = 1.7$, CHCl_3). IR (KBr): 2922, 2854, 2381, 1733, 1458, 1271, 1030, 970, 604, 494. $^1\text{H-NMR}$: 5.79–5.72 (m , 1 H); 5.16–5.04 (m , 3 H); 4.23–4.10 (m , 4 H); 3.72–3.57 (m , 2 H); 3.02–2.80 (m , 2 H); 2.44–2.32 (m , 2 H); 1.89–1.80 (m , 1 H); 1.75–1.66 (m , 1 H); 1.40–1.33 (m , 6 H). $^{13}\text{C-NMR}$: 165.9; 133.0; 118.0; 72.7; 63.0; 58.2; 38.7; 36.2; 33.5; 16.2. ESI-HR-MS: 295.1310 ($[M + \text{H}]^+$, $\text{C}_{12}\text{H}_{24}\text{O}_6\text{P}^+$; calc. 295.1305).

(6*S*)-5,6-Dihydro-6-(prop-2-en-1-yl)-2H-pyran-2-one (**7**). To a stirred soln. of iodoxybenzoic acid (3.7 g, 13.22 mmol) in dry DMSO (10 ml), was added a soln. of **6** (2.6 g, 8.84 mmol) in anh. THF (35 ml) at r.t. and stirred for 6 h. After completion of the reaction (TLC monitoring), the mixture was quenched with H_2O (20 ml) and filtered through *Celite*. The filtrate was extracted with AcOEt (3×50 ml). The combined org. phase was washed with brine (75 ml), dried (Na_2SO_4), and concentrated, and the resulting crude aldehyde (2.75 g) was used as such without further purification for the next step. To a suspension of NaH (0.32 g, 13.62 mmol) in dry THF (60 ml), the crude aldehyde (2.75 g, 8.06 mmol) in THF (200 ml) was added at 0° , and the mixture was stirred for 2 h. After completion of the reaction (TLC monitoring), it was quenched with H_2O (30 ml). THF was removed, the aq. layer extracted with AcOEt (3×50 ml), the combined org. phase dried (Na_2SO_4) and concentrated, and the residue purified by CC (SiO_2): **7** (0.64 g, 68% over two steps). Colorless liquid. R_f (AcOEt/hexane 3:7) 0.7. $[\alpha]_{\text{D}}^{25} = +84$ ($c = 2.1$, CHCl_3). IR (KBr): 2923, 2855, 1726, 1459, 1280, 1071, 526. $^1\text{H-NMR}$: 6.87–6.79 (m , 1 H); 6.00 ($dt, J = 9.8, 1.5$, 1 H); 5.88–5.79 (m , 1 H); 5.20–5.11 (m , 2 H); 4.49–4.42 (m , 1 H); 2.62–2.40 (m , 2 H); 2.37–2.31 (m , 2 H). $^{13}\text{C-NMR}$: 164.2; 144.9; 132.2; 121.2; 118.8; 77.0; 39.0; 28.6. ESI-MS: 138 (M^+).

(2*R*)-3,6-Dihydro-6-oxo-2H-pyran-2-acetaldehyde (**8**). To a stirred soln. of **7** (0.2 g, 1.42 mmol) in dioxane/ H_2O 3:1 (8 ml), 2,6-lutidine (0.31 g, 2.89 mmol), OsO_4 (0.007 g, 0.028 mmol), and NaIO_4 (1.23 g, 5.79 mmol) were added. The mixture was stirred at r.t. for 4 h (TLC monitoring). The mixture was quenched with H_2O (10 ml) and extracted with CH_2Cl_2 (3×30 ml). The combined org. phase was washed with brine (50 ml), dried (Na_2SO_4), and concentrated, and the resulting crude **8** (208 mg, 91%) was used as such without further purification in the next step.

((1*E*)-3-[(Trimethylsilyloxy]buta-1,3-dien-1-yl]benzene (**9**). To a stirred soln. of (3*E*)-4-phenylbut-3-en-2-one (0.5 g, 3.44 mmol) and Et_3N (0.47 ml, 5.17 mmol) in freshly prepared anh. CH_2Cl_2 (10 ml) at -10° was added dropwise $\text{CF}_3\text{SO}_3\text{SiMe}_3$ (0.8 ml, 4.10 mmol). The mixture was stirred at -10° for 30 min and quenched with sat. aq. NaHCO_3 soln. The aq. layer was extracted with CH_2Cl_2 (2×25 ml), the combined org. phase dried (Na_2SO_4) and concentrated at r.t., and the resulting crude **9** (0.46 g) was used as such for the next step without purification.

(6*R*)-5,6-Dihydro-6-[(2*S*,5*E*)-2-hydroxy-4-oxo-6-phenylhex-5-en-1-yl]-2H-pyran-2-one (**1**). Aldehyde **8** (0.208 g, 1.4 mmol) and silyl enol ether **9** (0.46 g, 2.12 mmol) were taken up in freshly prepared anh. CH_2Cl_2 (20 ml), and the mixture was cooled to -78° . $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.30 ml, 2.12 mmol) in freshly prepared anh. CH_2Cl_2 (5 ml) was added slowly. The mixture was stirred at -78° for additional 2 h and quenched with sat. aq. NaHCO_3 soln. (10 ml). The aq. layer was extracted with CH_2Cl_2 (2×25 ml), the combined org. phase washed with H_2O (40 ml) and brine (40 ml), dried (Na_2SO_4), and concentrated, and the residue purified by CC (SiO_2): **1** (382 mg, 81% over two steps). White solid. R_f (AcOEt/hexane 1:3) 0.3. M.p. 73–74°. $[\alpha]_{\text{D}}^{25} = +82.4$ ($c = 1.0$, CHCl_3) ($[\alpha]_{\text{D}}^{20} = +84$ ($c = 0.231$, CHCl_3)). IR (KBr):

3453, 3028, 2924, 2854, 1712, 1604, 1384, 1252, 1049, 781, 508. ¹H-NMR: 7.58 (*d*, *J* = 16.0, 1 H); 7.56–7.52 (*m*, 2 H); 7.43–7.36 (*m*, 3 H); 6.94–6.91 (*m*, 1 H); 6.77–6.68 (*d*, *J* = 16.0, 1 H); 6.02 (*dd*, *J* = 9.8, 2.0, 1 H); 4.85–4.75 (*m*, 1 H); 4.54–4.46 (*m*, 1 H); 2.93 (*dd*, *J* = 17.3, 3.0, 1 H); 2.81 (*dd*, *J* = 17.3, 9.0, 1 H); 2.44–2.30 (*m*, 2 H); 1.93–1.78 (*m*, 2 H). ¹³C-NMR: 200.3; 164.2; 145.2; 143.8; 134.0; 130.8; 128.9; 128.4; 125.9; 121.3; 74.8; 63.9; 46.8; 41.6; 29.9. ESI-HR-MS: 309.1102 ($[M + Na]^+$, C₁₇H₁₈NaO₄⁺; calc. 309.1109).

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