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Note

A Concise Synthetic Approach to β,γ-Dehydrocurvularin: Synthesis of (±)-Di-*O*-Methyl-β,γ-dehydrocurvularin

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A concise synthesis of di-*O*-methyl-β,γ-dehydrocurvularin, the di-*O*-methylated derivative of the naturally occurring nematicidal macrolide, β,γ-dehydrocurvuralin, was accomplished by starting from a commercially available aromatic carboxylic acid in a three-step sequence consisting of esterification, Friedel-Crafts acylation, and microwave-promoted ring-closing metathesis.

Key words: curvuralin; nematicide; macrolide; ring-closing metathesis; microwave-promoted reaction

β,γ-Dehydrocurvularin (**1**), which belongs to the curvularin family of polyketides represented by curuvularin (**3**), has recently been isolated from the culture broth of a species of *Aspergillus* collected in Tottori, Japan, and its structure was determined by spectroscopic methods (Fig. 1).[1] The octaketidic macrolide exhibited considerable nematicidal activity against the root-lesion nematode, *Pratylenchus penetrans*, without any inhibitory effects on the growth of lettuce seedlings, and is therefore expected to be a promising lead for practical nematicides. This agriculturally intriguing biological activity as well as the substantially unstable β,γ-unsaturated ketone structural unit incorporated in **1** stimulated our interest in its total synthesis.[2,3] In this note, we describe part of our synthetic efforts toward **1**, which successfully resulted in a short-step synthesis of its di-*O*-methylated derivative [(±)-**2**] possessing the same carbon framework as that of **1**.

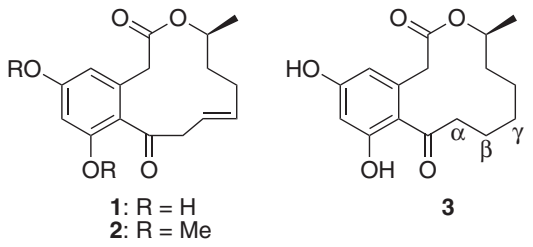
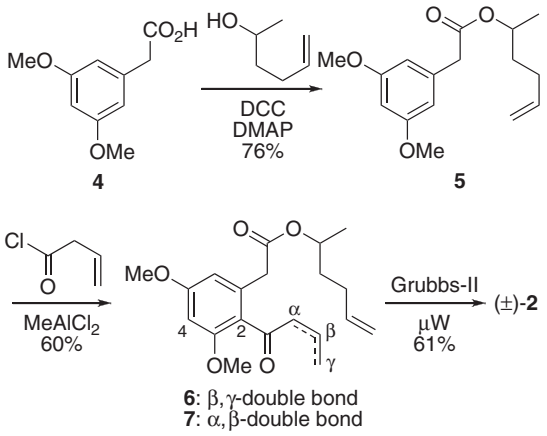


Fig. 1. β,γ-Dehydrocurvularin (**1**) and Related Compounds.



Scheme 1. Synthesis of Di-*O*-Methyl-β,γ-dehydrocurvularin.

Commercially available aromatic carboxylic acid **4** and 5-hexen-2-ol were condensed under conventional conditions (DCC/DMAP/toluene) to give ester **5** in a 76% yield (Scheme 1). The Friedel-Crafts acylation of **5** with 3-butenoyl chloride in the presence of $MeAlCl_2$ as a Lewis acid catalyst proceeded regioselectively to afford desired C2-acylation product **6** in a 60% yield; fortunately, this unstable β,γ-unsaturated ketone (**6**) survived the acidic reaction conditions, and no detectable degree of double-bond migration to generate the more stable conjugated enone(s) (**7**) took place. The next ring-closing metathesis step was first attempted by using the first-generation Grubbs catalyst.[4–6] Despite extensive examination of various reaction conditions [amount of the catalyst (5–50 mol %), solvent (CH_2Cl_2 or toluene), concentration (5 mM–150 mM), reaction temperature (room temperature to reflux), and reaction time (up to 1 week)], no desired product [(±)-**2**] could be obtained, resulting in the recovery of the starting material (**6**), generation of **7**, or the formation of a complex mixture. Similar attempts with the second-generation Grubbs catalyst (Grubbs-II) were also unsuccessful in

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most cases, but we noticed that a small amount of (±)-**2** was produced together with **7** (main product) when the reaction mixture was refluxed in toluene for 4 hours in the presence of 20 mol % of the Grubbs-II catalyst. Encouraged by this result, we next tried the application of microwave irradiation which has recently been shown to dramatically promote a variety of reactions including cross-metathesis and has been successfully applied to the syntheses of many natural products.[7,8] To our delight, microwave irradiation of the mixture of **6** and the Grubbs-II catalyst (35 mol %) in toluene at 90 °C greatly facilitated the intramolecular metathesis reaction, furnishing a 61% yield of the desired product (±)-**2** in only 15 min. Furthermore the newly formed double bond of the cyclization product was installed exclusively in the *E*-form, as assigned from the ^{1}H-NMR coupling constant (15.3 Hz) between the two olefinic protons.

In conclusion, an efficient synthesis of di-*O*-methyl-β,γ-dehydrocurvularin [(±)-**2**)] was achieved by starting from commercially available carboxylic acid **4** in only three steps. Unfortunately, removal of the methyl protecting groups of the two phenolic hydroxyls with several Lewis acids to deliver naturally occurring **1** was not successful. Synthetic efforts toward **1** are now underway by using other protecting groups and (*S*)-5-hexen-2-ol, and the results will be reported in due course.

Experimental

IR spectra were recorded as films by a Jasco FT/IR-4100 spectrometer. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian Gemini 2000 spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C) or by a Varian Unity plus-600 spectrometer (600 MHz for ^{1}H and 150 MHz for ^{13}C). Mass spectra were obtained with a Jeol JMS-700 spectrometer operated in the EI mode. Silica gel 60N (Kanto Kagaku; spherical neutral, 100–210 µm particle size) was used for column chromatography.

*1-Methyl-4-pentenyl (3,5-dimethoxyphenyl)acetate (**5**).* To a stirred solution of 5-hexen-2-ol (300 mg, 3.00 mmol) in toluene (40 ml) were successively added 1,3-dicyclohexylcarbodiimide (1.24 g, 6.01 mmol), 4-(dimethylamino)pyridine (147 mg, 1.20 mmol) and 3,5-dimethoxybenzoic acid (1.18 g, 6.48 mmol) at room temperature under a nitrogen atmosphere. After being stirred for 1 h, the mixture was filtered through a pad of Celite. The filter cake was washed with a mixture of hexane and ether (2:1), and the combined filtrate was concentrated *in vacuo*. The residue was chromatographed over SiO_2 (hexane/EtOAc, 20:1) to give **5** (635 mg, 76%) as a colorless oil. IR ν_{max} cm^{-1}: 3075 (w), 1731 (s), 1597 (s), 1205 (m), 1156 (s); ^{1}H-NMR (300 MHz) δ: 1.22 (3H, d, J = 6.3 Hz), 1.52–1.64 (1H, m), 1.65–1.76 (1H, m), 1.94–2.12 (2H, m), 3.53 (2H, s), 3.78 (6H, s), 4.87–4.97 (1H, m), 4.94 (1H, dm, J = 10.2 Hz), 4.96 (1H, dq, J = 16.8, 1.6 Hz), 5.76 (1H, ddt, J = 16.8, 10.2, 6.9 Hz), 6.37 (1H, t, J = 2.3 Hz), 6.45 (2H, d, J = 2.3 Hz); ^{13}C-NMR (75 MHz) δ: 19.8, 29.5, 35.0, 42.0, 55.2, 71.0, 99.2, 107.3, 115.0, 136.4, 137.8, 160.9, 171.1; HRMS m/z (M^+): calcd. for $C_{16}H_{22}O_4$, 278.1518; found, 278.1519.

*1-Methyl-4-pentenyl [2-(3-butenoyl)-3,5-dimethoxyphenyl)]acetate (**6**).* To a stirred solution of **5** (300 mg, 1.08 mmol) in CH_2Cl_2 (100 ml) were successively added 3-butenoyl chloride (345 mg, 3.30 mmol) and $MeAlCl_2$ (1.0 M in hexane, 4.3 ml, 4.3 mmol) at 0 °C under a nitrogen atmosphere. After being stirred for 1 h at 0 °C, the mixture was quenched with water and extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (hexane/EtOAc, 5:1) to give **6** (228 mg, 60%) as a colorless oil. IR ν_{max} cm^{-1}: 3080 (w), 1732 (s), 1685 (m), 1640 (w), 1604 (s), 1318 (s), 1156 (s); ^{1}H-NMR (300 MHz) δ: 1.22 (3H, d, J = 6.3 Hz), 1.52–1.62 (1H, m), 1.62–1.74 (1H, m), 2.00–2.11 (2H, m), 3.630 (2H, dt, J = 6.9, 1.6 Hz), 3.631 (2H, s), 3.82 (3H, s), 3.83 (3H, s), 4.84–4.96 (1H, m), 4.95 (1H, dm, J = 10.3 Hz), 5.00 (1H, dq, J = 17.2, 1.6 Hz), 5.13 (1H, dq, J = 17.2, 1.6 Hz), 5.14 (1H, dm, J = 10.3 Hz), 5.78 (1H, ddt, J = 17.2, 10.3, 6.6 Hz), 6.00 (1H, ddt, J = 17.2, 10.3, 6.9 Hz), 6.38 (1H, d, J = 2.3 Hz), 6.40 (1H, d, J = 2.3 Hz); ^{13}C-NMR (75 MHz) δ: 19.8, 29.5, 34.9, 39.1, 49.0, 55.3, 55.5, 71.0, 97.4, 107.9, 115.0, 118.0, 119.1, 131.8, 135.2, 137.9, 159.1, 161.7, 171.1, 204.3; HRMS m/z (M^+): calcd. for $C_{20}H_{26}O_5$, 346.1780; found, 346.1784.

*Di-O-Methyl-β,γ-dehydrocurvularin [(±)-**2**].* A test tube containing a solution of **6** (50.0 mg, 0.144 mmol) and the 2nd-generation Grubbs catalyst (43 mg, 51 µmol) in toluene (5 ml) under a nitrogen atmosphere was capped with a septum, and inserted into the cavity of Discover Microwave System apparatus (from CEM). The mixture was irradiated at 150 W for 15 min (90 °C internal temperature, controlled and monitored with the standard infrared temperature control system for the Discover System) before being cooled to room temperature and concentrated *in vacuo*. The residue was chromatographed over SiO_2 (hexane/EtOAc, 10:1) to give (±)-**2** (28.0 mg, 61%) as a colorless oil. IR ν_{max} cm^{-1}: 1729 (vs), 1690 (s), 1605 (vs), 1313 (s), 1203 (s), 1157 (s); ^{1}H-NMR (600 MHz) δ: 1.17 (3H, d, J = 5.9 Hz) 1.55–1.62 (1H, m), 1.62–1.69 (1H, m), 1.97–2.05 (1H, m), 2.22–2.30 (1H, m), 3.20–3.48 (2H, br m), 3.54 (1H, br d, J = 15.7 Hz), 3.59 (1H, br d, J = 15.7 Hz), 3.80 (3H, s), 3.83 (3H, s), 5.02–5.10 (1H, m), 5.24 (1H, dt, J = 15.3, 7.3 Hz), 5.44–5.56 (1H, m), 6.39 (1H, d, J = 2.3 Hz), 6.47 (1H, d, J = 2.3 Hz); ^{13}C-NMR (150 MHz) δ: 21.0, 30.5, 33.7, 37.9, 48.9, 55.4, 55.6, 72.4, 97.5, 108.0, 120.0 (two overlapping peaks), 133.9, 137.2, 157.5, 161.1, 170.8, 204.8; HRMS m/z (M^+): calcd. for $C_{18}H_{22}O_5$, 318.1467; found, 318.1472.

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