Concise Total Synthesis of Curvulone B

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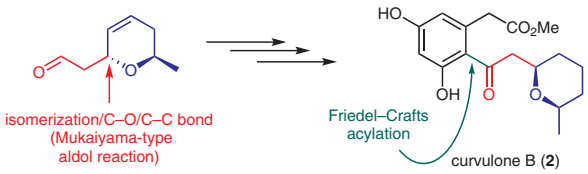

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Abstract A concise and convergent stereoselective synthesis of curvulone B is described. The synthesis utilized a tandem isomerization followed by C–O and C–C bond-forming reactions following Mukaiyama-type aldol conditions for the construction of the *trans*-2,6-disubstituted dihydropyran ring system as the key steps. Other important features of this synthesis are a cross-metathesis, epimerization, and Friedel–Crafts acylation.

Key words curvulone B, natural products, Mukaiyama–aldol reaction, Friedel–Crafts acylation reaction

Marine fungi have been long recognized as a rich source of novel secondary metabolites with such biological properties as antitumor, phytotoxic, or antifungal activities, as well as cytotoxicity against human cancer cell lines.[1] In connection with the search for biologically active metabolites from fungi, Krohn and Kurtán and their co-workers isolated two new curvularin-type metabolites, curvulone A (**1**) and curvulone B (**2**; Figure 1) from a *Curvularia sp.* obtained from the marine alga *Gracilaria folifera*.[1] Curvulone B (**2**) features a 2,6-disubstituted *cis*-tetrahydropyran ring, and displays antitumor, antifungal, and cytotoxic activities.[2]

The structure of curvulone B was determined by 2D NMR spectroscopy, and its absolute configuration was deduced by comparison of the experimental electronic circular dichroism spectra in acetonitrile with the Boltzman-averaged spectrum.[3] Total syntheses of curvulone B (**2**) have been reported by the groups of Takahashi,[2] Bates,[4] and, more recently, He.[5] None of these syntheses involved fewer than ten linear steps, and all employed an intramolecular oxa-Michael addition for the formation of THP ring.

We recently reported the synthesis of 2,6-*trans*-disubstituted tetrahydropyrans with a keto functionality by means of a Mukaiyama-type aldol reactions of 1-phenyl-1-(trimethylsiloxy)ethylene with six-membered cyclic hemiacetals in the presence of iodine.[6] As a further application of this Mukaiyama-type aldol reaction, and as a part of our ongoing research on the total synthesis of biologically active natural products containing pyran rings,[7] we report an efficient and convergent synthesis of curvulone B in seven steps.

Our retrosynthetic analysis of curvulone B is outlined in Scheme 1. It was envisaged that curvulone B might be prepared by a Friedel–Crafts acylation reaction of aromatic ester **3** and the acid fragment **4** (Scheme 1). We planned to obtain intermediate **4** from the *trans*-2,6-disubstituted dihydropyran **5** that, in turn, would be accessed from a δ-hydroxy α,β-unsaturated aldehyde through tandem isomeri-

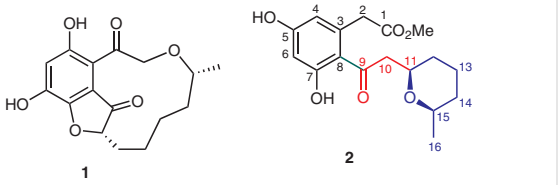
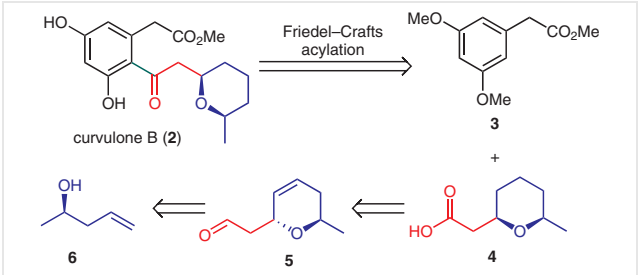


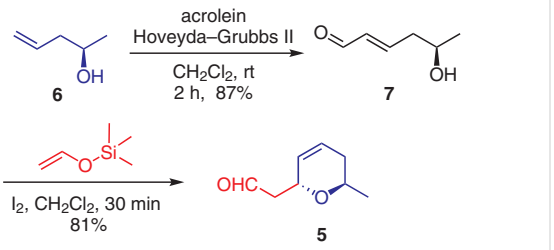
Figure 1 Structures of curvulone A (**1**) and curvulone B (**2**)



Scheme 1 Retrosynthetic analysis of curvulone B (**2**)

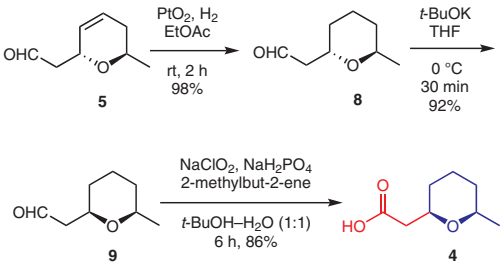
zation followed by C–O and C–C bond-forming reactions of a silyl enol ether under Mukaiyama-type aldol reaction conditions. The δ-hydroxy α,β-unsaturated aldehyde would be obtained from the commercially available chiral homoallylic alcohol **6**.

The synthesis of the key intermediate **5** began with the commercially available homoallylic alcohol **6** and acrolein, which, on treatment with the Hoveyda–Grubbs catalyst (10 mol%) in CH_2Cl_2 gave the cross-metathesis[8] product, the δ-hydroxy α,β-unsaturated aldehyde **7**, in 87% yield (Scheme 2). Tandem isomerization followed by a C–O and C–C bond-formation protocol under Mukaiyama-type conditions was performed by treating **7** with trimethyl(vinyloxy)silane in the presence of a catalytic amount of molecular iodine in anhydrous CH_2Cl_2 at room temperature to furnish the *trans*-2,6-disubstituted-3,4-dihydropyran **5** as the sole product in 81% yield.[6,9,10]



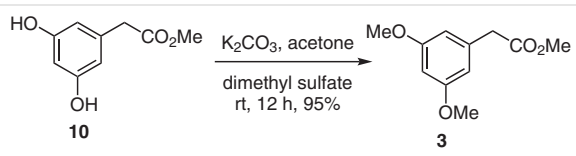
Scheme 2 Synthesis of compound **5**

The next task was to reduce the internal double bond and then to perform the isomerization reaction. Accordingly, the double bond in compound **5** was reduced in the presence of a catalytic amount of Adams's catalyst under hydrogen in anhydrous ethyl acetate to furnish compound **8** in excellent yield (Scheme 3). Epimerization was performed by a retro-oxa-Michael/oxa-Michael reaction with potassium *tert*-butoxide in THF at 0 °C; this reaction was highly stereoselective, favoring the desired C-β-epimer **9**, which was obtained in 92% yield.[11] Acid **4**, a key fragment for the Friedel–Crafts acylation strategy, was then synthesized in 86% yield from *cis*-pyran aldehyde **9** by Pinnick oxidation[12] with $NaClO_2$, NaH_2PO_4, *t*-BuOH–H_2O (1:1), and 2-methylbut-2-ene.



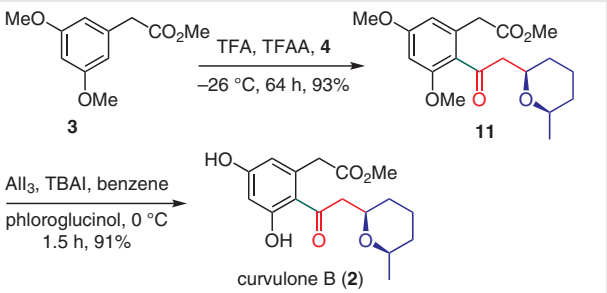
Scheme 3 Synthesis of compound **4**

The aromatic coupling fragment **3** was synthesized by methylation of commercially available methyl 2-(3,5-dihydroxyphenyl)acetate (**10**) with potassium carbonate and dimethyl sulfate in acetone to afford methyl 2-(3,5-dimethoxyphenyl)acetate (**3**) in 95% yield (Scheme 4).[13]



Scheme 4 Synthesis of fragment **3**

With *cis*-pyran acid **4** and methyl 2-(3,5-dimethoxyphenyl)acetate (**3**) in hand, our next objective was to combine both fragments by using the key Friedel–Crafts acylation reaction. Accordingly, treatment of *cis*-pyran acid **4** with methyl 2-(3,5-dimethoxyphenyl)acetate (**3**) in TFA/TFAA, afforded the desired ketone **11** in 93% yield (Scheme 5).[14]



Scheme 5 Completion of the total synthesis of curvulone B (**2**)

The structure of compound **11** was confirmed by extensive NMR experiments, including DQF-COSY, TOCSY, NOESY, HSQC, and HMBC experiments. The distinctive AB spin system of double doublets at δ = 2.97 and 3.04 ppm, due to 10-H and 10-H′ displaying a HMBC correlation with the carbonyl carbon (δ = 204.3 ppm), was used to initiate the assignments. The DQF-COSY experiment helped us to assign the protons from 11-H to 15-H and the 16-CH_3 protons. The 2-CH_2 protons appear as a broad singlet at δ = 3.60 ppm. The nOe correlations 11-H/15-H, 11-H/13-H, 13-H/15-H, and 12-H′/14-H′ strongly supported the *syn* orientation of the 11-H and 15-H protons, as well as the $^{14}C_{11}$ chair conformation of the six-membered ring. Furthermore, nOe correlations between 10-H/2-CH_2, 2-CH_2/4-H, and 7′-OCH_3/10-H provided strong evidence that the pyran ring occupies an position *ortho* to methyl ester of the benzene ring, providing firm support for the proposed structure of **11** (Figure 2).

Finally, demethylation of the methoxy group of **11** was successfully achieved under Maier's conditions (AlI_3, TBAI, phloroglucinol)[15] in benzene at 0 °C to furnish curvulone B (**2**) in 91% yield.[16] The spectroscopic and analytical data for synthetic compound **2** were in good agreement with those reported for the natural product.[1]

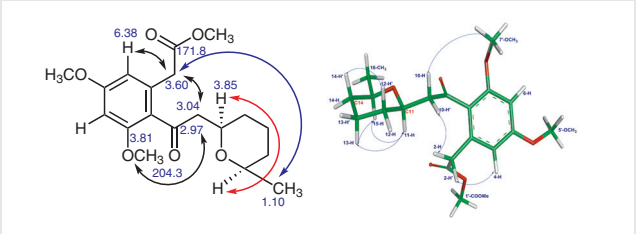


Figure 2 Energy-minimized structure of **11**, along with key nOe correlations (double-headed arrows)

In summary, a concise and stereoselective synthesis of the curvulone B (**2**) was achieved in seven steps and a 46% overall yield by using iodine-catalyzed tandem isomerization followed by C–O and C–C bond-formation through a Mukaiyama-type aldol reaction for the construction of the *trans*-2,6-disubstituted dihydropyran ring system as the key step. The other important reactions involved in the current synthetic approach were cross-metathesis, epimerization, and Friedel–Crafts acylation reactions.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1297-6838.

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(10) **[(2*R*,6*R*)-6-Methyl-5,6-dihydro-2*H*-pyran-2-yl]acetaldehyde (5)**
I_2 (0.89 g, 3.51 mmol) was added to a stirred solution of aldehyde **7** (2.0 g, 17.54 mmol) and trimethyl(vinyloxy)silane (3.85 mL, 26.31 mmol) in anhyd CH_2Cl_2 (50 mL) at 0 °C, and the mixture was allowed to warm to rt. When the reaction was complete (TLC), it was quenched with sat. aq $Na_2S_2O_3$ (30 mL), and the mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, EtOAc–hexane (1:5)] to give a pale-yellow liquid; yield: 1.99 g (81%); $[\alpha]_D^{20}$ –68.0 (*c* = 0.85, $CHCl_3$).
IR (neat): 3033, 2971, 2928, 1721, 1636, 1373, 1187, 1137, 1090 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.81 (s, 1 H), 5.87 (m, 1 H), 5.70 (d, *J* = 11.7 Hz, 1 H), 4.78 (m, 1 H), 3.83 (m, 1 H), 2.76 (ddd, *J* = 16.2, 8.8, 3.0 Hz, 1 H), 2.55 (dd, *J* = 16.2, 4.7 Hz, 1 H), 2.06–1.91 (m, 2 H), 1.21 (d, *J* = 6.2 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.0, 127.5, 125.2, 67.6, 64.1, 47.9, 31.5, 20.6. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_8H_{12}NaO_2$: 163.0728; found: 163.0724.

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(16) **Curvulone B (2)**
A suspension of Al powder (192 mg, 7.37 mmol) in anhyd benzene (5 mL) was treated with I_2 (0.7 g, 2.74 mmol) under argon, and the violet mixture was stirred under reflux for 30 min until the mixture became colorless. The mixture was then cooled to 0 °C, and TBAI (12.7 mg, 0.034 mmol) and phloroglucinol (108 mg, 0.85 mmol) were added, followed by a solution of **11** (60 mg, 0.17 mmol) in anhyd benzene (2 mL) added in one portion. The resulting green–brown suspension was stirred for 30 min at 0 °C. When the reaction was complete (TLC), it was quenched with sat. aq aqueous $Na_2S_2O_3$ (10 mL), and the mixture was diluted with EtOAc (15 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (25 mL), filtered, dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by column

chromatography [silica gel, EtOAc–hexane (1:1)] to give a colorless liquid; yield: 50 mg (91%); $[\alpha]_D^{20}$ –18.2 (*c* = 0.2, EtOH).
IR (neat): 3410, 2928, 1713, 1613, 1451, 1334, 1166 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.79 (s, 1 H), 6.28 (d, *J* = 2.3 Hz, 1 H), 6.22 (d, *J* = 2.3 Hz, 1 H), 6.08 (br s, 1 H), 4.13 (brtt, *J* = 10.5, 2.3 Hz, 1 H), 3.92 (d, *J* = 16.5 Hz, 1 H), 3.70 (s, 3 H), 3.57 (m, 1 H), 3.51 (d, *J* = 16.6 Hz, 1 H), 3.30 (dd, *J* = 14.3, 10.1 Hz, 1 H), 2.56 (dd, *J* = 14.3, 3.1 Hz, 1 H), 1.85 (m, 1 H), 1.65–1.50 (m, 3 H), 1.42 (m, 1 H), 1.25 (m, 1 H), 1.17 (d, *J* = 6.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.2, 172.4, 159.4, 135.7, 120.7, 111.7, 104.0, 77.8, 74.8, 52.0, 49.0, 39.7, 32.6, 30.7, 23.1, 21.5. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{23}O_6$: 323.1489; found: 323.1494.