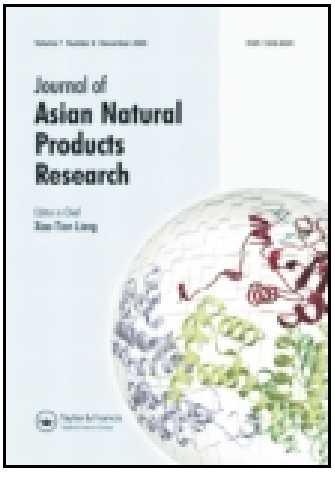

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Synthesis and antifungal activity of 7-methyl-7-hydroxy-2,3-benzo[c]octa-1,6-olide

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The racemic 7-methyl-7-hydroxy-2,3-benzo[c]octa-1,6-olide, the analog of natural product (6*R*)-3,7-dimethyl-7-hydroxy-2-octen-1,6-olide, was totally synthesized using easily available (*E*)-2-(2-carboxyvinyl)benzoic acid as a raw material in nine-step reactions including three key steps of Wittig reaction, epoxidation, and cyclization, with an overall yield of 10.3%. The bioassay results showed that (±)-**2** exhibited stronger antifungal activity than the natural product (±)-**1** and (*R*)-**1** against *Alternaria solani* with an EC_{50} value of 27.36 μg/ml.

Keywords: 7-methyl-7-hydroxy-2,3-benzo[c]octa-1,6-olide; total synthesis; lactonization of epoxy carboxylic acid; antifungal activity

1. Introduction

(6*R*)-3,7-Dimethyl-7-hydroxy-2-octen-6-olide (**1**) was an unique natural product with seven-membered lactone which was first isolated from the honey bee fungal entomopathogen *Ascosphaera apis* [1] as well as the fruit of plant *Litsea cubeba* in Tibet [2], and exhibited good antifungal and antioxidant activities. In order to compare the antifungal activity differences against phytopathogens, the racemate of 3,7-dimethyl-7-hydroxy-2-octen-6-olide was totally synthesized via lactonization of epoxy carboxylic acid as a synthetic strategy [3], and (6*R*) and (6*S*) isomers were totally synthesized via Sharpless asymmetry dihydroxylation and acid-catalyzed cyclization as the key steps [4]. Their photostabilities were problem due to the double bond in the molecule, and the structure needs to be modified to enhance the activity and stability such as in the development of pyrethroid insecticides. We hoped to replace the double bond with a benzene ring, and the novel aromatic analog **2** was designed and could meet the requirements, and have more possibility to modify the structure in the future. Due to target molecule (**2**) having a very unique structure of a seven-membered lactone ring with an isopropanol side chain, the several protocols including oxidative lactonization (Scheme 1), Baeyer–Villiger oxidation (Scheme 1), the palladium-catalyzed carbonylative annulation of internal alkynes, the ring-closing metathesis synthesis of unsaturated lactones, and enzymatic synthesis were not suitable for synthesis [5–11]. In this paper, we choose easily available (*E*)-2-(2-carboxyvinyl) benzoic acid as the starting material and synthesized the racemic title compound **2** through nine-step reactions with overall yields of 10.3% (Scheme 2), and its antifungal activity was evaluated.

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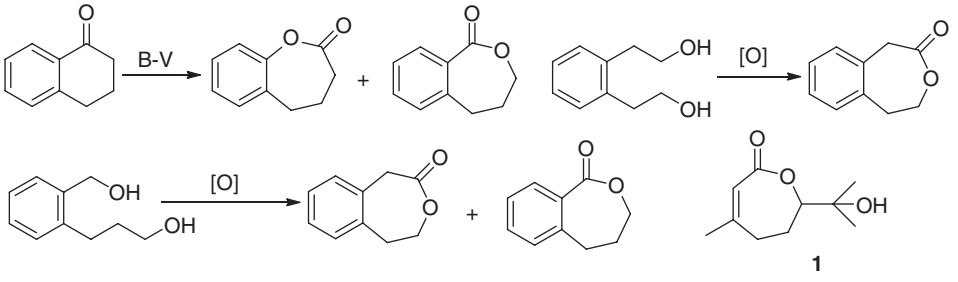
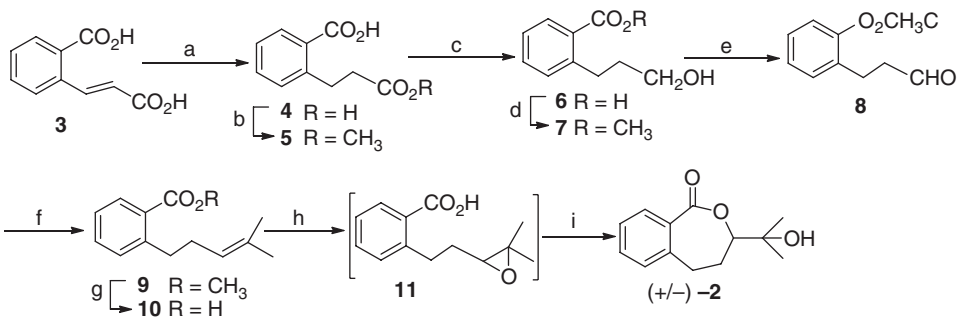


Scheme 1. Synthetic methods of benzoxepinone isomers [10,11] and structure of **1**.

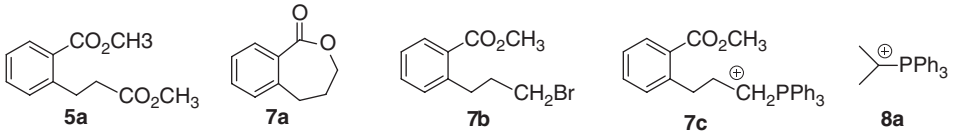
2. Results and discussion

Lactonization of epoxy carboxylic acid was selected as the synthetic strategy as we did in the previous paper [3], and the olefins **9** or **10** were the key intermediates. Based on the retro-synthesis analysis and the protocol in the reference [12], the (*E*)-2-(2-carboxyvinyl) benzoic acid was selected as the starting material and transferred into compound **4** in $PdCl_2$–HCO_2H–NaOH system in 95% yield, and the catalyst $PdCl_2$ was recovered and re-used five times without yield decreasing. The monoester **5** could be prepared via **4** and methanol in the presence of concentrated H_2SO_4 at ambient temperature in 87% yield with about 8% byproduct of diester **5a** (Scheme 2). The monoester **5** was selectively reduced by $LiBH_4$ to give alcohol **6**, which was further esterified with methanol in the presence of concentrated H_2SO_4 at reflux temperature to afford alcohol **7** in 68% yield along with 10% byproduct of lactone **7a** (Scheme 2). Then alcohol **7** was converted into bromide **7b**, which could not be efficiently transferred into the Wittig reagent **7c** in various conditions due to the hindrance of *ortho* ester group in the benzene ring (Scheme 3), so our work of trying to prepare olefin **9** via the Wittig reaction of acetone and the Wittig reagent **7c** was unsuccessful.

After that, the alcohol **7** was oxidized into aldehyde **8**, which could react with the Wittig reagent **8a** to produce olefin **9** in 62% yield. The olefin **9** was readily hydrolyzed into the benzoic acid **10**. The benzoic acid **10** was epoxidized with



Scheme 2. Synthetic route of racemic compound **2**. Reaction conditions: (a) $PdCl_2$, HCO_2H, NaOH, 65°C; (b) CH_3OH, H_2SO_4, r.t.; (c) N_2, $LiBH_4$,100°C; (d) CH_3OH, H_2SO_4; (e) PCC, CH_2Cl_2, r.t.; (f) N_2, *n*-BuLi, $Ph_3PCH(CH_3)_2Br$; (g) NaOH, reflux; (h) AcO_2H, r.t.; (i) CSA, r.t.



Scheme 3. The byproducts and intermediates mentioned in synthesis of compound **2**.

peracetic acid to give epoxy benzoic acid **11** without further purification, and it could be cyclized into the racemic lactone **2** in the presence of catalytic quantity of camphorsulfonic acid by the novel synthetic strategy of lactonization of epoxy carboxylic acid [3] (Scheme 2). After the synthesis of **2** was successfully completed in this paper, we found that the synthetic route is still too long and more efficient approaches were required and used in the syntheses of the other substituted aromatic analogs, and the progress was made in our laboratory.

The preliminary bioassay showed that the (±)**-2**, (±)**-1**, and (*R*)**-1** exhibited good antifungal activity against *Alternaria solani* with EC_{50} values of 27.36, 50.48, and 42.20 μg/ml [13], respectively. These results indicated that compound **2** had stronger antifungal activity than the natural compound **1**.

3. Experimental

3.1 General experimental procedures

Melting points were measured on a Yanagimoto apparatus (Yanagimoto MFG Co., Kyoto, Japan) and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Brüker DPX 300 NMR Spectrometer (Brüker Biospin Co., Stuttgart, Germany) with $CDCl_3$ as the solvent and tetramethylsilane as the internal standard. HR-MS were obtained on a Brüker Apex II mass spectrometer (Brüker Co., Bremen, Germany) using nitrobenzoyl alcohol and sodium chloride as matrices. The solvents were analytical grade and newly distilled before usage.

3.2 General procedure for title compound 7-methyl-7-hydroxy-2,3-benzo[c]octa-1,6-olide

3.2.1 Synthesis of 2-(2-carboxyethyl) benzoic acid (4)

About 484 mg (2.6 mmol, 10 mol%) of $PdCl_2$, 5.01 g (*E*)-2-(2-carboxyvinyl) of benzoic acid **3** (26.1 mmol), 300 ml of 2.5 mol/l NaOH solution, and 4.0 ml of formic acid (104 mmol, 4.0 equiv.) were added into a 500-ml flask, stirred, and heated to 65°C for 24 h. After removal of the catalyst, the mother liquid was extracted with diethyl ether. The water phase was acidified carefully with HCl to pH 1–2, and the precipitate was filtered. The mother liquid was re-extracted with AcOEt and the solvent was removed in vacuo. The solid was combined and re-crystallized with alcohol to give a white solid 4.91 g, yield 95%, m.p. 164–166°C (167–169°C [12]). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 2.54 (t, $J = 6.9$ Hz, 2H), 3.12 (t, $J = 6.9$ Hz, 2H), 7.28–7.35 (m, 2H), 7.44–7.45 (m, 1H), 7.79–7.81 (m, 1H), 12.50 (br, 2H).

3.2.2 Synthesis of 2-(2-carboxyethyl) benzoic acid monoester (5)

About 10.01 g (51.6 mmol) of **4**, 150 ml of MeOH, and 2 ml of 98% H_2SO_4 were added into a 250-ml flask and stirred for 2 h at ambient temperature. Then the solvent was removed, and 20 ml of water and 40 ml of 1.0 mol/l NaOH solution were added. The obtained mixture was stirred and adjusted to pH 8–9 with the saturated $NaHCO_3$ solution. The solution was extracted with diethyl ether, and the organic phase was

dried. The byproduct **5a** was obtained as a little yellow liquid in 8% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.68 (t, $J = 6.9$ Hz, 2H), 3.26 (t, $J = 6.9$ Hz, 2H), 3.65 (s, 3H), 3.89 (s, 3H), 7.24–7.29 (m, 2H), 7.40–7.45 (m, 1H), 7.89–7.92 (m, 1H). Then the water phase was acidified carefully with HCl to pH 1–2, and the precipitate appeared and was filtered. The solid was dried to give a white solid **5** (9.37 g), yield 87%, m.p. 79–82°C (79–81°C [12]). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.72 (t, $J = 7.5$ Hz, 2H), 3.36 (t, $J = 7.5$ Hz, 2H), 3.68 (s, 3H), 7.26–7.32 (m, 2H), 7.47–7.52 (m, 1H), 8.07–8.10 (m, 1H), 12.00 (br, 1H).

3.2.3 *Synthesis of 2-(3-hydroxypropyl) benzoic acid (**6**)*

Under the N_2 atmosphere, 75 ml of 1,4-dioxane and 2.36 g of $LiBH_4$ were added into a 250-ml flask, stirred 2 h at ambient temperature, and then 7.45 g (35.8 mmol) of **5** solution in 1,4-dioxane was dropped in 30 min. After this, the flask was heated to 100°C for 6 h in an oil bath. Then the solvent was removed and the residue was poured into 100 g of ice water. The solution was carefully adjusted to pH 9–10 with the saturated NaOH solution. The solution was extracted with diethyl ether and the organic phase was casted out. The water phase was acidified carefully with HCl to pH 1–2. The solution was re-extracted with AcOEt, and the organic phase was dried over $MgSO_4$ and the solvent was removed in vacuo to afford a white solid **6** (5.17 g), yield 80%, m.p. 55–58°C (55–65°C [12]). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.90–1.99 (m, 2H), 3.08–3.15 (m, 2H), 3.68 (t, $J = 6.0$ Hz, 2H), 4.52 (s, 1H), 7.27–7.32 (m, 2H), 7.44–7.51 (m, 1H), 7.99–8.06 (m, 1H), 12.14 (br, 1H).

3.2.4 *Synthesis of methyl 2-(3-hydroxypropyl) benzoate (**7**)*

About 5.17 g (51.6 mmol) of **6**, 100 ml of MeOH, and 2 ml of 98% H_2SO_4 were added into a 250-ml flask, and the mixture was stirred and heated to reflux for 36 h. Cooling to room temperature, the solvent was removed, and 20 ml of water and 40 ml of 1.0 mol/l NaOH solution were added. The solution was stirred and adjusted to pH 8–9 with the saturated $NaHCO_3$ solution. Then the solution was extracted with AcOEt, the organic phase was dried over $MgSO_4$, and the solvent was removed. The residue was chromatographed on a silica gel column and washed with petroleum ether–AcOEt (20:1, 0.8% AcOH) to give a colorless oily liquid **7a** (0.89 g), yield 18%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.04–2.17 (m, 2H), 2.90 (t, $J = 7.2$ Hz, 2H), 4.16 (t, $J = 6.3$ Hz, 2H), 7.20–7.27 (m, 1H), 7.34–7.39 (m, 1H), 7.46–7.51 (m, 1H), 7.71–7.73 (m, 1H). The residue was continued to wash and afforded a colorless oily liquid **7** (3.78 g), yield 68%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.85–1.94 (m, 2H), 2.71 (s, 1H), 3.05 (t, $J = 7.2$ Hz, 2H), 3.61 (t, $J = 6.0$ Hz, 2H), 3.88 (s, 3H), 7.21–7.28 (m, 2H), 7.39–7.45 (m, 1H), 7.85–7.88 (m, 1H), identical to those in Ref. [14].

3.2.5 *Synthesis of methyl 2-(3-bromopropyl) benzoate (**7b**)*

About 300 mg (1.4 mmol) of **7**, 570 mg (2.1 mmol, 1.5 equiv.) of PBr_3, 25 ml of diethyl ether, and five drops of pyridine were added into a 50-ml flask. The solution was stirred and heated to reflux for 24 h. The solid was filtered and the solvent was removed, then 50 ml of CH_2Cl_2 was added and the solution was washed with saturated $NaHCO_3$ and NaCl solutions. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was chromatographed on a silica gel column and washed with petroleum ether–AcOEt (15:1) to give a colorless oily liquid **7b** (250 mg), yield 52%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.12–2.21 (m, 2H), 3.09 (t, $J = 7.5$ Hz, 2H), 3.42 (t, $J = 6.9$ Hz, 2H), 3.87 (s, 3H), 7.22–7.28 (m, 2H), 7.39–7.44 (m, 1H), 7.88–7.91 (m, 1H), identical to those in Ref. [15].

3.2.6 Synthesis of methyl 2-(3-oxopropyl) benzoate (**8**)

About 571 mg (2.65 mmol) of PCC, 1.5 g of silica gel, and 20 ml of CH_2Cl_2 were added into a 50-ml flask. The mixture was stirred and the solution of 343 mg (1.77 mmol) of **7** in 15 ml of CH_2Cl_2 was dropped. After that, the solution was stirred at ambient temperature overnight, the solvent was removed, and the residue was chromatographed on a silica gel column and washed with petroleum ether–AcOEt (20:1, 15:1, 10:1) to give a colorless oily liquid **8** (285 mg), yield 84%. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.78–2.84 (m, 2H), 3.27 (t, $J = 7.5$ Hz, 2H), 3.89 (s, 3H), 7.25–7.31 (m, 2H), 7.41–7.44 (m, 1H), 7.91–7.94 (m, 1H), 9.82 (brs, 1H), identical to those in Ref. [16].

3.2.7 Synthesis of methyl 2-(4-methyl-3-penten-1-yl) benzoate (**9**)

Under N_2 atmosphere, 859 mg **8a** (2.25 mmol, 1.5 equiv.), which was prepared following the procedure in Ref. [16], was added into a 100-ml flask. The flask was sealed, and 50 ml of diethyl ether was injected. The mixture was cooled to -10°C. Then 0.75 ml of 2.5 mol/l *n*-BuLi solution was injected, and the solution was stirred 1 h at ambient temperature. The solution of 286 mg (1.49 mmol) of **8** in 10 ml of diethyl ether was added by injection, and the mixture was stirred 3 h at ambient temperature. The solvent was removed and the residue was chromatographed on a silica gel column, washed with petroleum ether–AcOEt (40:1, 30:1, 20:1) to give a colorless oily liquid **9** (135 mg), yield 62%. IR ν_{max} (cm^{-1}): 2926, 1725, 1601, 1434, 1258, 1080, 752, 710. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.51 (s, 3H), 1.67 (s, 3H), 2.24–2.32 (m, 2H), 2.97 (t, $J = 7.5$ Hz, 2H), 3.88 (s, 3H), 5.18 (t, $J = 7.0$ Hz, 1H), 7.20–7.25 (m, 2H), 7.37–7.43 (m, 1H), 7.83–7.86 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.5, 25.6, 30.2, 34.4, 51.8, 123.7, 125.7, 129.7, 130.4, 131.0, 131.7, 132.1, 143.9, 168.2. HR-ESI-MS *m/z*: 219.1380 $[M + H]^+$ (calcd for $C_{14}H_{19}O_2$, 219.1379).

3.2.8 Synthesis of 2-(4-methyl-3-penten-1-yl) benzoic acid (**10**)

About 280 mg (1.28 mmol) of **9**, 0.5 g of NaOH, 10 ml of water, and 15 ml of methanol were added into a 50-ml flask. The solution was stirred and heated to reflux for 12 h, the solvent was removed and 20 ml of water was added, and then extracted with diethyl ether. The water phase was adjusted to pH 1–2 with HCl solution and extracted with AcOEt. The organic phase was dried over $MgSO_4$ and the solvent was removed. The residue was chromatographed on a silica gel column and washed with petroleum ether–AcOEt (100:1, 0.5% AcOH) to give a white solid **10** (165 mg), yield 85%, m.p. 61–63°C. IR ν_{max} (cm^{-1}): 2924, 2641, 1694, 1269, 920, 747, 702, 659. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.54 (s, 3H), 1.69 (s, 3H), 2.28–2.35 (m, 2H), 3.06 (t, $J = 7.5$ Hz, 3H), 5.21 (m, 1H), 7.26–7.31 (m, 2H), 7.44–7.50 (m, 1H), 8.02–8.05 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 17.4, 25.7, 30.3, 34.7, 123.7, 125.9, 128.3, 131.4, 131.6, 132.4, 132.8, 145.2, 173.4. HR-ESI-MS *m/z*: 205.1222 $[M + H]^+$ (calcd for $C_{13}H_{17}O_2$, 205.1223).

3.2.9 Synthesis of racemic 7-methyl-7-hydroxy-2,3-benzo[c]octa-1,6-olide (*R,S*-**2**)

About 3.06 g (15 mmol) of **10** and 75 ml of CH_2Cl_2 were added into a 250-ml flask. The solution was stirred and 10 ml of peracetic acid solution was added, and 3.3 g of Na_2CO_3 was added three times in 15 min interval. After 2 h, the solution was adjusted to pH 5–6 with the diluted HCl solution and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and the solvent was removed to afford **11** without further purification. Then acid **11** was dissolved in 75 ml of CH_2Cl_2 in a 150-ml flask, 200 mg of camphorsulfonic acid was added, and the

mixture was stirred overnight at ambient temperature. The solution was washed with saturated $NaHCO_3$ and NaCl solutions. The organic phase was dried over $MgSO_4$ and the solvent was removed. The residue was chromatographed on a silica gel column and washed with petroleum ether–AcOEt (20:1, 12:1, 8:1) to afford a colorless oily liquid **2** (1.72 g), yield 52% for two steps. IR ν_{max} (cm^{-1}): 3417, 2973, 1715, 1455, 1299, 942, 757, 641. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.25 (s, 6H), 1.92–2.01 (m, 1H), 2.25–2.36 (m, 1H), 2.77–2.84 (m, 1H), 2.89–2.96 (m, 1H), 3.87 (dd, $J = 13.5$, 4.8 Hz, 1H), 7.21–7.28 (m, 1H), 7.35–7.40 (m, 1H), 7.46–7.52 (m, 1H), 7.71–7.74 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.3, 26.2, 28.5, 29.5, 71.6, 84.2, 127.3, 128.6, 130.1, 131.3, 132.7, 138.2, 171.2. HR-ESI-MS *m/z*: 221.1172 $[M + H]^+$ (calcd for $C_{13}H_{17}O_3$, 221.1172).

In summary, the racemic 7-methyl-7-hydroxy-2,3-benzo[c]octa-1,6-olide (**2**) was synthesized through nine-step reactions with an overall yield of 10.3%. The (±)-**2** exhibited stronger antifungal activity against *A. solani* with an EC_{50} value of 27.36 μg/ml than the natural product (±)-**1** and (R)-**1** with EC_{50} values of 50.48 and 42.20 μg/ml, respectively.

Acknowledgments

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