

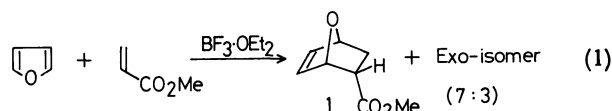
Synthetic Studies of Diels–Alder Adduct of Furan. Formal Total Synthesis of (±)-Avenaciolide

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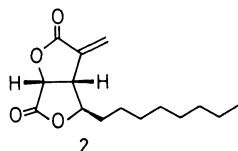
The *endo*-Diels–Alder adduct of furan with methyl acrylate was transformed into a bis- γ -lactone derivative which is a well-known precursor for the synthesis of (±)-avenaciolide. The route involves 13 steps and the overall yield was 17.9%.

The 7-oxabicyclo[2.2.1]heptene derivatives, which can be prepared by Diels–Alder reaction of furan with appropriate dienophiles, are versatile precursors for the synthesis of various important natural products.¹⁾ However, mainly due to the sluggish reactivity of furan itself, such derivatives have remained difficult to access.

Recently, we demonstrated a practical method for the preparation of the Diels–Alder adduct (1) between furan and methyl acrylate under $\text{BF}_3 \cdot \text{OEt}_2$ -catalyzed conditions (Eq. 1).²⁾ Herein, we wish to report on the



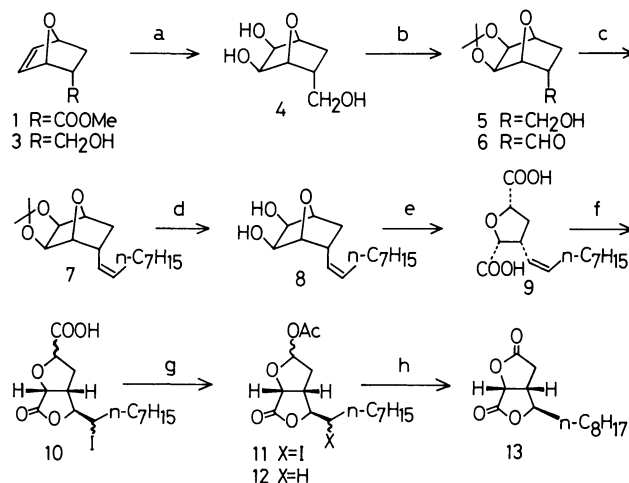
stereoselective synthesis of the antifungal metabolite (±)-avenaciolide (2).³⁾ The strategy of the synthesis



relies on the advantageous structure of adduct (1) which has two of three stereocenters in the target system and the stereoselective iodolactonization for the preparation of the remaining one (Scheme 1).

The *endo*-ester (1) was transformed into the alcohol (5) via the triol (4) in 77.8% overall yield. Swern oxidation⁴⁾ of this alcohol under carefully controlled conditions gave cleanly aldehyde (6) without epimerization,⁵⁾ this was treated with Wittig reagent to give 7 as the sole product. The structure of the olefin was determined as having a *cis*-configuration by ^1H NMR measurement ($J=11$ Hz). Deprotection of acetonide, NaIO_4 cleavage, and Jones oxidation provided dicarboxylic acid (9). Since this product was rather unstable, presumably due to its sterically congested structure, the crude sample was used directly for the further experiment.

For the construction of the remained stereocenter we applied the well-known chemistry of iodolactonization.⁶⁾ Thus, by treatment with $\text{KI}-\text{I}_2$ 9 was smoothly converted into the iodo lactone carboxylic acid (10). The relative stereochemistry of this product could not be determined at this stage, but we expected the reaction to yield predominantly compound (10) with the



Scheme 1. Reagents and Conditions.

(a): 1) LiAlH_4 , Et_2O , 2) OsO_4 , 30% H_2O_2 , RT, (b): 1) 2,2-dimethoxypropane, MeOH , pyridinium *p*-toluenesulfonate, RT, 2) $(\text{COCl})_2$, DMSO , Et_3N , -78°C , (c): $\text{Ph}_3\text{P}^+n\text{-C}_8\text{H}_{17}\text{Br}^-$, $n\text{-BuLi}$, THF , RT, overnight, (d): 2M HCl , MeOH , (e): 1) NaIO_4 , $\text{THF}-\text{H}_2\text{O}$, 2) $\text{CrO}_3-\text{H}_2\text{SO}_4$, acetone, (f): $\text{KI}-\text{I}_2$, NaHCO_3 , $\text{THF}-\text{H}_2\text{O}$, RT, overnight, (g): 1) $\text{Pb}(\text{OAc})_4$, C_6H_6 , reflux, 2 h, 2) $n\text{-Bu}_3\text{SnH}$, $\text{AIBN}(\text{cat.})$, C_6H_6 , reflux, 20 h, (h): 1) K_2CO_3 , $\text{MeOH}-\text{H}_2\text{O}$, 2) $\text{CrO}_3-\text{H}_2\text{SO}_4$, acetone.

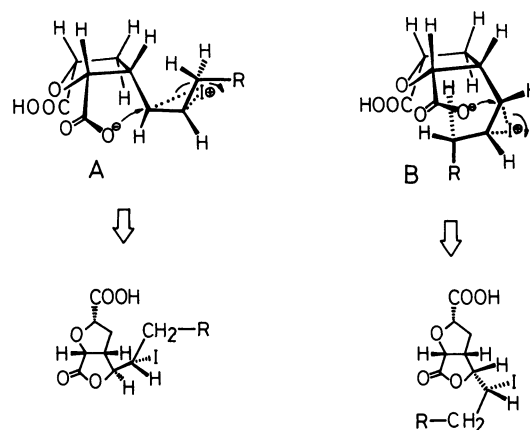


Fig. 1.

desired stereochemistry based on the consideration of molecular models. As illustrated in Fig. 1, there are two stereoselections for this cyclization process in which the ring closure should take a favored 5-*Exo-Trig* path⁷⁾ and the nucleophile should cleave the iod-

onium ring by rear-side attack. When the reaction takes place through an intermediate **A**, the desired product will be obtained. While the intermediate **B** will give the undesired one which possesses an isoavenaciolide skeleton. The obvious relative steric comfort will favor the intermediate **A** over **B**. We recognized that this expectation is correct after completion of our work (vide infra).

In analogy with Masamune's earlier work,⁸⁾ bis- γ -lactone formation was performed by a 4-step process; decarboxylative acetylation with lead tetraacetate, deiodination with tributyltin hydride, hydrolysis of acetate, and Jones oxidation. Purification by silica-gel column chromatography gave the desired bis- γ -lactone (**13**) as a single product in 32.3% overall yield from **8** and the structure was confirmed by the comparison with an authentic sample.⁹⁾ This result means that as expected the iodolactonization proceeded in a desired fashion.¹⁰⁾ Introduction of the α -methylene group on **13** was reported previously,³⁾ so this work constitutes a formal total synthesis of ($\pm$)-avenaciolide.

By using optically pure starting material¹¹⁾ it will be possible to synthesize avenaciolide in the natural form.

Experimental

General. All boiling and melting points are uncorrected. ¹H NMR spectra were obtained on a JEOL-MH-100 spectrometer using TMS as the internal standard. ¹³C NMR spectra were obtained at 25.05 MHz on a JEOL-FX-100 spectrometer. The IR spectra were measured with a JASCO infrared spectrophotometer Model IRA-1 or A-302 and the high resolution mass spectra on a JEOL-HX-100 spectrometer.

TLC was conducted using Merck's precoated Kieselgel 60 F-254 plates (0.25 mm) and for column chromatography, Wakogel C-200 was employed.

Ether and THF were distilled from sodium benzophenone ketyl. Benzene was distilled from sodium metal. Dichloromethane, triethylamine and DMSO were distilled over CaH₂. Acetone was distilled once from CrO₃ and stored over molecular sieves 3A.

Reduction of 1: To a stirred suspension of 360 mg (9.5 mmol) of LiAlH₄ in 36 ml of dry Et₂O at 0°C was added a solution of **1** (1.68 g, 11 mmol) in 12 ml of dry Et₂O. After being stirred at room temperature for 5 h, the reaction mixture was diluted with Et₂O (20 ml) and quenched at 0°C by addition of a minimum amount of water. After drying with anhydrous MgSO₄ the mixture was filtered through Celite and the solid washed well with AcOEt. Evaporation of the solvent gave 1.38 g (100%) of almost pure alcohol (**3**).

3: TLC *R*_f=0.34 (Et₂O); Bp 110 °C/5 mmHg (1 mmHg = 133.322 Pa; bath temperature); IR (neat) 3400 and 1035 cm⁻¹; ¹H NMR (CDCl₃) δ =0.64 (1H, dd, *J*=12, 4 Hz), 1.96 (1H, ddd, *J*=12, 9, 4.5 Hz), 2.2–2.6 (1H, m), 3.10 (1H, t, *J*=10 Hz), 3.4–3.7 (2H, m), 4.90, 4.98 (each 1H, dd, *J*=4.5, 1.5 Hz), 6.26, 6.37 (each 1H, dd, *J*=6, 1.5 Hz). Found: C, 66.47; H, 8.03%. Calcd for C₇H₁₀O₂: C, 66.64; H, 7.99%.

Formation of Triol (4) with OsO₄: To a solution of **3** (1.19 g, 9.4 mmol) in 35 ml of acetone and 9 ml of Et₂O were successively added 11.5 ml aqueous solution of OsO₄ (0.055

mmol) and 3.8 ml of 30% H₂O₂ at 0°C and the resulting brownish solution was stirred at room temperature overnight. At the end of the reaction the solution color disappeared. After evaporation of the solvent, finally azeotropically with toluene, the residue was purified by silica-gel column chromatography, elution with AcOEt–MeOH (9:1), and recrystallized from AcOEt–MeOH to give 1.22 g (80.7%) of triol (**4**) as colorless needles.

4: TLC *R*_f=0.34 (AcOEt–MeOH, 9:1); Mp 101.0–101.5 °C; IR (nujol) 3400 and 1075 cm⁻¹; ¹H NMR (DMSO-*d*₆-CDCl₃) δ =0.93 (1H, dd, *J*=12.5, 5 Hz), 1.82 (1H, ddd, *J*=12.5, 12, 6 Hz), 2.0–2.4 (1H, br m), 2.7 (1H, br), 3.3–4.0 (4H, m), 4.0–4.4 (4H, m). Found: C, 52.47; H, 7.59%. Calcd for C₇H₁₂O₄: C, 52.49; H, 7.55%.

Formation of Acetonide (5): A mixture of **4** (1.22 g, 7.63 mmol) and 2,2-dimethoxypropane (5.6 ml) in 2.4 ml of dry MeOH containing a catalytic amount of pyridinium *p*-toluenesulfonate was stirred at room temperature overnight. After evaporation of most of the organic solvent the residue was poured into CH₂Cl₂ and washed successively with water, satd NaHCO₃, and satd NaCl, dried with MgSO₄, and evaporated. Recrystallization from hexane–Et₂O gave 1.47 g (96.4 %) of the acetonide (**5**).

5: TLC *R*_f=0.63 (AcOEt–MeOH, 9:1); Mp 104.5–107 °C; IR (nujol) 3460 and 1055 cm⁻¹; ¹H NMR (CDCl₃) δ =0.89 (1H, dd, *J*=12.5, 5.5 Hz), 1.29, 1.48 (each 3H, s), 1.89 (1H, ddd, *J*=12.5, 12, 6 Hz), 2.1–2.5 (1H, m), 2.6 (1H, br), 3.51 (1H, dd, *J*=11, 8.5 Hz), 3.72 (1H, dd, *J*=11, 7 Hz), 4.15 (1H, d, *J*=6 Hz), 4.33 (1H, d, *J*=2 Hz), 4.39 (1H, br s), 4.55 (1H, d, *J*=6 Hz). Found: C, 59.76; H, 7.97%. Calcd for C₁₀H₁₆O₄: C, 59.98; H, 8.05%.

Swern Oxidation of the Alcohol (5): To a stirred suspension of 0.39 ml (4.5 mmol) of oxalyl dichloride in 7 ml of dry CH₂Cl₂ at –78 °C was added 0.64 ml (9.0 mmol) of dry DMSO. After being stirred at –78 °C for 10 min, to the suspension was added a solution of **5** (500 mg, 2.5 mmol) in 3 ml of dry CH₂Cl₂ at the same temperature. After being stirred at –78 °C for 1 h,¹²⁾ to the reaction mixture was added 2.44 ml (17.5 mmol) of dry Et₃N. The reaction mixture was diluted with 120 ml of AcOEt and quickly washed with cold satd NaHCO₃ and satd NaCl, dried with MgSO₄, and evaporated. The crude product was purified by silica-gel column chromatography and elution with hexane–AcOEt (1:2), to give 395 mg (80%) of pure aldehyde (**6**) as colorless crystals.

6: TLC *R*_f=0.25 (Et₂O); Mp 93–94.5 °C (from hexane–acetone); IR (nujol) 1710, 1210, and 1065 cm⁻¹; ¹H NMR (CDCl₃) δ =1.26, 1.46 (each 3H, s), 1.71–1.88 (2H, m), 3.08 (1H, m), 4.19 (2H, s), 4.45 (1H, dd, *J*=4, 2 Hz), 4.69 (1H, dd, *J*=6, 1.5 Hz), 9.17 (1H, d, *J*=1.5 Hz); MS (30 eV) *m/z* (rel intensity) 183 (M⁺–CH₃, 100), 111 (8), 95 (3), 83 (31), 66 (20), 59 (22), 55 (7), 43 (27). Found: *m/z* 198.0871. Calcd for C₁₀H₁₄O₄: M, *m/z* 198.0892.

Wittig Reaction of the Aldehyde (6): To 22 ml of dry THF solution of Ph₃P⁺*n*-C₈H₁₇Br[–] (4.1 g, 9.0 mmol)¹³⁾ was added 4.9 ml (8.0 mmol) of butyllithium at 0°C under N₂ and the resultant reddish solution was stirred at room temperature for 1 h. To this solution 395 mg (2.0 mmol) of **6** in 4.4 ml of dry THF was introduced at –20 °C by using cannula and the mixture was stirred at room temperature overnight under N₂. After quenching by careful addition of satd NaCl at 0°C, the insoluble substance which formed was filtered through Celite and washed with AcOEt. After evaporation of most of the organic solvent, the residue was

extracted with AcOEt. The combined extracts were washed with satd NaCl, dried with MgSO₄, and evaporated. The crude product was purified by silica-gel column chromatography, elution with hexane-AcOEt (9:1), to give 586 mg (100%) of **7** as a colorless oil.

7: TLC R_f =0.18 (hexane-AcOEt, 9:1); IR (neat) 1455, 1370, 1210, and 1070 cm⁻¹; ¹H NMR (CCl₄) δ =0.90 (3H, t, J =6 Hz), 1.18, 1.37 (each 3H, s), 1.31 (10H, br s), 2.2–1.6 (4H, m), 2.83 (1H, m), 4.04, 4.08 (each 1H, d, J =3 Hz), 4.21, 4.33 (each 1H, d, J =6 Hz), 5.09 (1H, dd, J =11, 9.5 Hz), 5.43 (1H, dt, J =11, 7.5 Hz).

Formation of Diol (8): A mixture of **7** (610 mg, 2.07 mmol) and 8.7 ml of 2M HCl (1M=1 mol dm⁻³) in 8.7 ml of MeOH was refluxed overnight under N₂. After evaporation of MeOH, the aqueous layer was extracted with AcOEt. The combined extracts were washed with satd NaHCO₃ and satd NaCl, dried with MgSO₄, and evaporated. Recrystallization from hexane-AcOEt gave 470 mg (89.2%) of diol (**8**).

8: TLC R_f =0.63 (AcOEt); Mp 77.5–78.5 °C; IR (nujol) 3400, 1460, 1205, 1080, 990, and 910 cm⁻¹; ¹H NMR (CDCl₃) δ =0.88 (3H, t, J =6 Hz), 1.27 (10H, br s), 1.6–2.2 (4H, m), 2.93 (1H, m), 3.2–3.6 (2H, m), 3.7–3.9 (1H, m), 4.0–4.2 (1H, m), 4.18, 4.33 (each 1H, d, J =6 Hz), 5.08 (1H, dd, J =10, 8 Hz), 5.50 (1H, dt, J =10, 8 Hz). Found: C, 70.90; H, 10.31%. Calcd for C₁₅H₂₆O₃: C, 70.83; H, 10.30%.

Formation of Dicarboxylic Acid (9): To a stirred solution of 660 mg (2.6 mmol) of **8** in 12 ml of THF was added at 0 °C 830 mg (3.88 mmol) of NaIO₄ in 3.5 ml of water. The resulting white creamy mixture was stirred at room temperature overnight. After evaporation of THF, the aqueous layer was saturated with NaCl and extracted with AcOEt. The combined extracts were washed with satd NaCl, dried with MgSO₄, and evaporated to give 700 mg of product: TLC R_f =0.33 (CHCl₃-AcOEt, 1:1).¹⁴

The product so obtained was dissolved in 15 ml of acetone and to this solution was added at -20 °C 5.2 ml of Jones reagent (1.25 M) and the mixture stirred at 0 °C for 20 min. After quenching by addition of MeOH, the mixture was diluted with 6M H₂SO₄. After evaporation of most of the organic solvent, the aqueous layer was extracted with AcOEt. The combined extracts were washed with satd NaCl, dried with MgSO₄, and evaporated to give 700 mg (94.9% crude overall yield from **8**) of dicarboxylic acid (**9**) as an oil: IR (neat) 3400–2800, 1730, 1365, and 1230 cm⁻¹. This sample was sufficiently pure judging from its TLC and ¹H NMR result and was used immediately for the next reaction.¹⁵

Formation of Iodo Lactone Acetate (11): To a stirred solution of 700 mg (2.47 mmol) of **9** in 30 ml of THF were successively added 2 ml aqueous solution of NaHCO₃ (2.07 g) and 4 ml aqueous solution of KI (2.05 g) and I₂ (1.81 g). Then the resulting black solution was stirred at room temperature overnight. After quenching the excess of I₂ by addition of aq Na₂S₂O₃ solution and evaporation of THF, the aqueous phase was saturated with NaCl and extracted thoroughly with AcOEt. The combined extracts were washed with satd NaCl, dried with MgSO₄, and evaporated to give 948 mg of iodo lactone carboxylic acid (**10**): IR (neat) 1785 and 1740 cm⁻¹.

The product (175 mg, 0.43 mmol) so obtained was dried azeotropically with toluene, and then dissolved in 4 ml of dry C₆H₆ and treated with 210 mg (0.47 mmol) of freshly recrystallized Pb(OAc)₄ under reflux for 2 h. After cooling the mixture was filtered through Celite and washed well with

Et₂O. Evaporation of the solvent gave another crop of precipitate. From the Et₂O soluble fraction 190 mg of iodo lactone acetate (**11**) was obtained as almost 1:1 mixture of acetate.

11: R_f =0.60 (Et₂O); IR (neat) 1790, 1750, and 1230 cm⁻¹; ¹H NMR (CDCl₃) δ =0.90 (3H, t, J =6 Hz), 1.31 (12H, br s), 1.95, 2.01 (total 3H, each s), 1.8–2.6 (3H, m), 2.8–3.2 (1H, m), 4.15 (1H, m), 4.75, 4.87 (total 1H, each d, J =8 Hz), 6.34 (1H, d, J =8 Hz). Found: m/z 424.0733. Calcd for C₁₆H₂₅O₅I: M, m/z 424.0747.

Formation of Bis-γ-Lactone (13): A mixture of 190 mg of **11**, 0.15 ml of *n*-Bu₃SnH, and a catalytic amount of α,α'-azobisisobutyronitrile in 4 ml of dry C₆H₆ was refluxed under N₂ for 20 h. Evaporation of the solvent gave 230 mg of crude product (**12**). This sample was used for the next reaction without further purification. In a separate experiment **12** was prepared in 43.3% overall yield from **8** as crystalline solid after purification by silica-gel column chromatography (elution with Et₂O).

12: R_f =0.48 and 0.44 (Et₂O); Mp 131–134 °C (from hexane-Et₂O); IR (CHCl₃) 1785, 1240, and 1185 cm⁻¹; ¹H NMR (CDCl₃) δ =0.90 (3H, t, J =6 Hz), 1.31 (12H, br s), 1.98, 2.04 (total 3H, each s), 1.8–2.6 (3H, m), 2.8–3.3 (1H, m), 4.2 (1H, m), 4.85, 4.97 (total 1H, each d, J =8 Hz), 5.75 (0.4H, m), 6.48 (0.6H, d, J =5 Hz). Found: m/z 255.1617. Calcd for C₁₆H₂₆O₅-COCH₃: M, m/z 255.1596.

The crude product so obtained was dissolved in 3 ml of MeOH and then treated with 0.8 ml aqueous solution of K₂CO₃ (270 mg). After stirring for 4 h, the mixture was acidified with 2M HCl and extracted with Et₂O. After evaporation of the solvent, the residue was dissolved in 3 ml of acetone and to this solution at 0 °C Jones reagent was added until the solution showed an orange color. After being stirred for 20 min at 0 °C, the excess reagent was decomposed with MeOH and the mixture extracted with AcOEt. The combined extracts were washed with water and satd NaCl, dried with MgSO₄, and evaporated to give the crude product. Purification by silica-gel column chromatography, elution with hexane-Et₂O (1:1), afforded 40 mg (32.3% overall yield from **8**) of **13** as a colorless oil.

13: R_f =0.43 (Et₂O); IR (neat) 1790, 1460, 1240, 1210, 1140, 1070, and 970 cm⁻¹; ¹H NMR (CDCl₃) δ =0.89 (3H, t, J =6 Hz), 1.29 (12H, br s), 1.71 (2H, m), 2.4–3.2 (3H, m), 4.25–4.45 (1H, m), 5.00 (1H, d, J =7.5 Hz); ¹³C NMR (CDCl₃) δ =14.0, 22.7, 25.0, 29.1 (×2), 29.3, 31.8, 32.8, 35.5, 40.2, 77.1, 85.0, 170.0, 173.8. Found: m/z 254.1493. Calcd for C₁₄H₂₂O₄: M, m/z 254.1518.

All these spectral data were in good agreement with those reported in the literature.^{3,9)}

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10) Although we could not detect an isomer in the reaction mixture of **13**, the possibility of the formation of this one, which would be derived from the intermediate **B** as shown in Fig. 1, can not be excluded completely. Unfortunately, however, at no stage we could clarify this problem because of the complexity of the ¹H NMR spectra. So the conclusion relies on the result of the last stage composition.

11) Optical resolution of the corresponding carboxylic acid is reported: see Ref. 1c.

12) When Et₃N was introduced after 30 min stirring, exclusive formation of the *exo*-aldehyde was observed. Data for *exo*-isomer: Mp 61–63 °C (from hexane-acetone); IR (nujol) 1725, 1215, 1165, 1095, 1075, and 1055 cm⁻¹; ¹H NMR (CDCl₃) δ=1.28, 1.47 (each 3H, s), 1.39–1.62 (1H, m), 2.05 (1H, ddd, J=13.5, 6, 4.5 Hz), 2.31 (1H, ddd, δ=9, 4.5, 2 Hz), 4.19 (2H, s), 4.49 (1H, d, J=6 Hz), 4.62 (1H, s), 9.57 (1H, d, J=2 Hz). Found: *m/z* 198.0896.

13) This reagent was prepared by refluxing 1-bromooctane with triphenylphosphine in dry C₆H₆ and washed well with C₆H₆. The product was a highly viscous oil. It was hard to purify, so was used as obtained.

14) This compound would exist in the hydrated form from ¹H NMR measurement.

15) The use of stored or chromatographed samples gave poor results.