December, 1986] © *1986 The Chemical Society of Japan* *Bull. Chem. Soc. Jpn.*, *59*, *3881—3884 (1986)* 3881

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

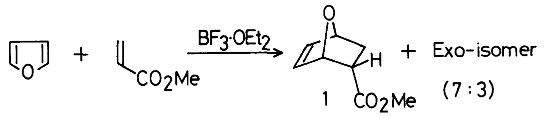
Hiyoshizo KOTSUKI,* Hiroyuki OHNISHI, Yasuhiro AKITOMO, Masamitsu OCHI
Department of Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780

(Received May 30, 1986)

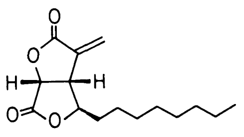
The *endo*-Diels–Alder adduct of furan with methyl acrylate was transformed into a bis-γ-lactone derivative which is a well-known precursor for the synthesis of (±)-avenaciolide. The route involves 13 steps and the overall yield was 17.9%.

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 $BF_3 \cdot OEt_2$-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).



(1)



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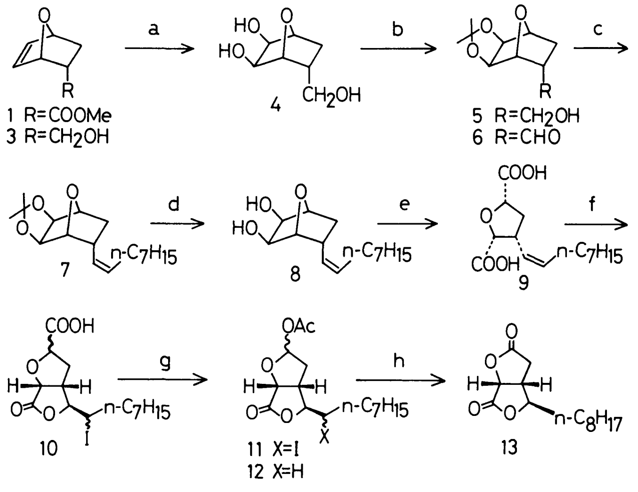
The *endo*-ester (**1**) was transformed into the alcohol (**5**) via the triol (**4**) in 77.8% overall yield. Swern oxidation[4] of this alcohol under carefully controlled conditions gave cleanly aldehyde (**6**) without epimerization,[5] this was treated with Wittig reagent to give **7** as the sole product. The structure of the olefin was determined as having a cis-configuration by ^{1}H 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 $KI-I_2$ **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 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* path[7] and the nucleophile should cleave the iod-



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) $(COCl)_2$, DMSO, Et_3N, −78°C, (c): $Ph_3P^+n\text{-}C_8H_{17}Br^-$, *n*-BuLi, THF, RT, overnight, (d): 2M HCl, MeOH, (e): 1) $NaIO_4$, THF–H_2O, 2) CrO_3–H_2SO_4, acetone, (f): $KI-I_2$, $NaHCO_3$, THF–H_2O, RT, overnight, (g): 1) $Pb(OAc)_4$, C_6H_6, reflux, 2 h, 2) $n\text{-}Bu_3SnH$, AIBN(cat.), C_6H_6, reflux, 20 h, (h): 1) K_2CO_3, MeOH–H_2O, 2) CrO_3–H_2SO_4, acetone.

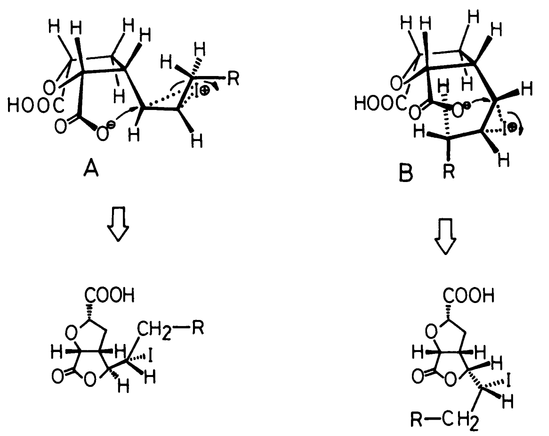


Fig. 1.

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 (±)-avenaciolide.

By using optically pure starting material[11] it will be possible to synthesize avenaciolide in the natural form.

Experimental

General. All boiling and melting points are uncorrected. ^{1}H NMR spectra were obtained on a JEOL-MH-100 spectrometer using TMS as the internal standard. ^{13}C 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 CaH_2. Acetone was distilled once from CrO_3 and stored over molecular sieves 3A.

Reduction of 1: To a stirred suspension of 360 mg (9.5 mmol) of $LiAlH_4$ in 36 ml of dry Et_2O at 0 °C was added a solution of **1** (1.68 g, 11 mmol) in 12 ml of dry Et_2O. After being stirred at room temperature for 5 h, the reaction mixture was diluted with Et_2O (20 ml) and quenched at 0 °C by addition of a minimum amount of water. After drying with anhydrous $MgSO_4$ 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 (Et_2O); Bp 110 °C/5 mmHg (1 mmHg =133.322 Pa; bath temperature); IR (neat) 3400 and 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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 $C_7H_{10}O_2$: C, 66.64; H, 7.99%.

Formation of Triol (4) with OsO_4: To a solution of **3** (1.19 g, 9.4 mmol) in 35 ml of acetone and 9 ml of Et_2O were successively added 11.5 ml aqueous solution of OsO_4 (0.055 mmol) and 3.8 ml of 30% H_2O_2 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}; ^{1}H NMR (DMSO-d^6-$CDCl_3$) 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 $C_7H_{12}O_4$: 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 CH_2Cl_2 and washed successively with water, satd $NaHCO_3$, and satd NaCl, dried with $MgSO_4$, and evaporated. Recrystallization from hexane-Et_2O 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}; ^{1}H NMR ($CDCl_3$) 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 $C_{10}H_{16}O_4$: 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 CH_2Cl_2 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 CH_2Cl_2 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 Et_3N. The reaction mixture was diluted with 120 ml of AcOEt and quickly washed with cold satd $NaHCO_3$ and satd NaCl, dried with $MgSO_4$, 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 (Et_2O); Mp 93—94.5 °C (from hexane-acetone); IR (nujol) 1710, 1210, and 1065 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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^+-CH_3, 100), 111 (8), 95 (3), 83 (31), 66 (20), 59 (22), 55 (7), 43 (27). Found: *m/z* 198.0871. Calcd for $C_{10}H_{14}O_4$: M, *m/z* 198.0892.

Wittig Reaction of the Aldehyde (6): To 22 ml of dry THF solution of $Ph_3P^+n\text{-}C_8H_{17}Br^-$ (4.1 g, 9.0 mmol)[13] was added 4.9 ml (8.0 mmol) of butyllithium at 0 °C under N_2 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 N_2. 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 $MgSO_4$, 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}; ^{1}H NMR (CCl_4) 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 N_2. After evaporation of MeOH, the aqueous layer was extracted with AcOEt. The combined extracts were washed with satd $NaHCO_3$ and satd NaCl, dried with $MgSO_4$, 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}; ^{1}H NMR ($CDCl_3$) 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 $C_{15}H_{26}O_3$: 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 $NaIO_4$ 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 $MgSO_4$, and evaporated to give 700 mg of product: TLC R_f=0.33 ($CHCl_3$-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 H_2SO_4. 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 $MgSO_4$, 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 ^{1}H 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 $NaHCO_3$ (2.07 g) and 4 ml aqueous solution of KI (2.05 g) and I_2 (1.81 g). Then the resulting black solution was stirred at room temperature overnight. After quenching the excess of I_2 by addition of aq $Na_2S_2O_3$ 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 $MgSO_4$, 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 C_6H_6 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 Et_2O. Evaporation of the solvent gave another crop of precipitate. From the Et_2O soluble fraction 190 mg of iodo lactone acetate (**11**) was obtained as almost 1 : 1 mixture of acetate.

11: R_f=0.60 (Et_2O); IR (neat) 1790, 1750, and 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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 $C_{16}H_{25}O_5I$: M, m/z 424.0747.

Fomation of Bis-γ-Lactone (13): A mixture of 190 mg of **11**, 0.15 ml of n-Bu_3SnH, and a catalytic amount of α,α'-azobisisobutyronitrile in 4 ml of dry C_6H_6 was refluxed under N_2 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 Et_2O).

12: R_f=0.48 and 0.44 (Et_2O); Mp 131—134 °C (from hexane-Et_2O); IR ($CHCl_3$) 1785, 1240, and 1185 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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 $C_{16}H_{26}O_5$-$COCH_3$: 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 K_2CO_3 (270 mg). After stirring for 4 h, the mixture was acidified with 2M HCl and extracted with Et_2O. 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 $MgSO_4$, and evaporated to give the crude product. Purification by silica-gel column chromatography, elution with hexane-Et_2O (1 : 1), afforded 40 mg (32.3% overall yield from **8**) of **13** as a colorless oil.

13: R_f=0.43 (Et_2O); IR (neat) 1790, 1460, 1240, 1210, 1140, 1070, and 970 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_{14}H_{22}O_4$: M, m/z 254.1518.

All these spectral data were in good agreement with those reported in the literature.[3,9]

The authors are grateful to Professor Takashi Tokoroyama of Osaka City University for his helpful suggestions. We are indebted to Dr. Takashi Sakai of Okayama University for spectral data of (±)-avenaciolide and bis-γ-lactone (**13**), and we also thank Dr. Ayumi Ohsaki of Kinki University for performing the high-resolution mass spectra measurements.

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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 ^{1}H 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 Et$_3$N 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}; ^{1}H NMR (CDCl$_3$) 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 C$_6$H$_6$ and washed well with C$_6$H$_6$. 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 ^{1}H NMR measurement.

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