A Convenient Synthesis Method for Methylenomycin B and Its Application to Methylenomycin A

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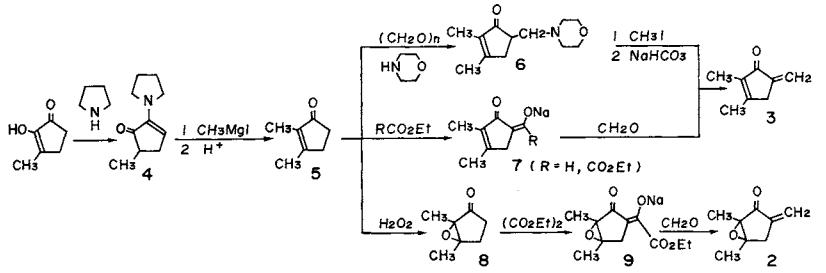
A convenient synthesis method for methylenomycin B and its homolog, methylenomycin A, has been developed. Methylenomycin B, 2,3-dimethyl-5-methylene-2-cyclopentenone (3) was synthesized: i) by methylation of Mannich derivative prepared from morpholine and 2,3-dimethyl-2-cyclopentenone (5) or ii) by treatment of formalin with sodio derivatives of 2,3-dimethyl-5-formyl-2-cyclopentenone (7a) and 2,3-dimethyl-5-ethoxalyl-2-cyclopentenone (7b), both of which were easily prepared from **5** and ethyl formate or ethyl oxalate. 2,3-Dimethyl-2,3-epoxy-5-methylenecyclopentanone (2) was similarly prepared from the epoxide compound of **5** and ethyl oxalate. The bioassay of methylenomycin B and its related compounds against bacteria (*B. subtilis, S. aureus, Ps. aeruginosa* and *E. coli*) was also conducted. Methylenomycin A (1) and its desepoxy compound (17) were also prepared from 4-carboxy-2,3-dimethyl-2-cyclopentenone (15) in the same procedure as described above.

Methylenomycin B[1,2] known as medicinally important cyclopentanone antibiotics as well as methylenomycin A (1)[1,3,4] was firstly isolated from a strain of *Streptomyces violaceoruber*[1] as an unstable oil and assigned to be 2,3-dimethyl-2,3-epoxy-5-methylenecyclopentanone (2) by a spectral similarities to methylenomycin A. However, Jernow *et al.*,[2] recently revised the structure (2) and claimed 2,3-dimethyl-5-methylene-2-cyclopentenone (3) for the material isolated as methylenomycin B.

The claimed structure of methylenomycin B as well as similar antibiotics, methylenomycin A and its desepoxy compound (17)[5] prompted us to establish a convenient synthesis for those compounds. We describe here a simple synthetic procedure for the compounds **1**, **2**, **3** and **17** as shown in Schemes 1 and 2.

I) Preparation of methylenomycin B (3) and its epoxy compound (2)

In planning the synthetic route for **2** and **3**, 2,3,-dimethyl-2-cyclopentenone (5) seemed to be the most attractive starting material (Scheme 1). The compound **5** was obtained in 82% yield by the reaction of methyl magnesium iodide and enamine (4) which was



SCHEME 1.

TABLE I. ANTIBACTERIAL ACTIVITIES OF METHYLENOMYCIN B AND ITS RELATED COMPOUNDS AGAINST VARIOUS BACTERIA*

Test bacteria	Compounds						
	 2	 3	 10	 11	 8	 5	 12
E. coli	+++	++	+	−	−	−	++
S. aureus	+++	++	+	−	+	+	++
B. subtilis	+++	++	+	−	−	−	++
Ps. aeruginosa	++	+	+	−	−	−	+

+++, zone size 15~20 mm; ++, zone size 9~14 mm; +, zone size 6~8 mm; −, no inhibition.

* Filter paper discs (5 mm diameter) saturated with the solution of the test compound (5 mg/ml in acetone) were placed on the agar plates after drying up the solvent. The plates were incubated at 35°C and the zone of inhibition around the discs were measured after 24 hr.

readily prepared from cyclotene.[6] A facile conversion of **5** to **3** was achieved by methylation of 2,3-dimethyl-5-morpholinomethyl-2-cyclopentenone (6) prepared from Mannich reaction of **5** and morpholine or by the treatment of formalin with sodio derivatives of 2,3-dimethyl-5-formyl-2-cyclopentenone (7a) and 2,3-dimethyl-5-ethoxaylyl-2-cyclopentenone (7b), both of which were conveniently prepared from **5** and ethyl formate or ethyl oxalate.

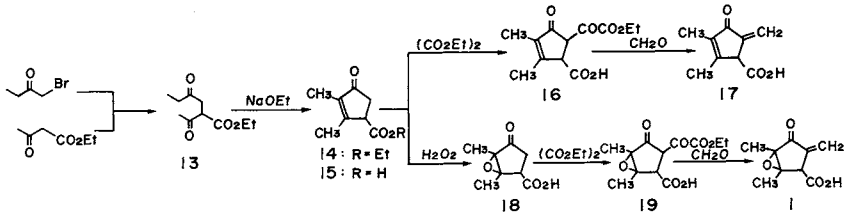
While 2,3-dimethyl-2,3-epoxycyclopentanone (8) prepared from **5** with basic hydrogen peroxide in methanol was allowed to react with ethyl oxalate to give the sodio derivative of 2,3-dimethyl-2,3-epoxy-5-ethoxalylcyclopentanone (9) and the treatment of **9** with formalin afforded the desired **2** in 26% yield from **5**.

A comparison of the spectral properties (IR and PMR) of **2** and **3** with those previously reported[1] revealed that **3** is consistent with the mateial isolated as methylenomycin B.[2]

The screening test of both compounds **2** and **3** against bacteria (*B. subtilis, S. aureus, Ps. aeruginosa* and *E. coli*) displayed a distinct antibacterial activities, whereas the conversion of exo methylene group to methyl group resulted in a considerable loss of antibacterial activities as indicated in Table I. Antibacterial activities of the other compounds pertaining to methylenomycin B were also shown for a rough comparison.

II) Preparation of methylenomycin A (1) and its desepoxy compound (17)

The strategy employed for the introduction of exo methylene group *via* sodio derivatives of α-formyl or α-ethoxalyl compound as described above was intrigued with a facile



SCHEME 2.

conversion of carboxylic acid (15) to **17** and epoxy carboxylic acid (18) to methylenomycin A (1) (Scheme 2).

Ethyl acetoacetate and 1-bromo-2-butanone[7] was allowed to react in a usual fashion to afford ethyl 2-acetyl-4-oxohexanoate (13) in 83% yield. Cyclization of **13** to 4-carbethoxy-2,3-dimethyl-2-cyclopentenone (14) was examined under several reaction conditions as follows. Under basic conditions employing NaH-THF, NaOEt-ether and NaH-benzene system gave no cyclized ester **14** but recovered starting material **13**. While the acidic conditions employing H_3PO_4–Ac_2O–AcOH and conc.HCl–EtOH system afforded neither **14** nor **13**. (unidentified less polar product was found on TLC) The effective reaction condition for this conversion was the system employing NaOEt–EtOH or *tert*-BuOK– *tert*-BuOH, but the reaction mixture of the latter was much contaminated with unreacted **13**. The best result was obtained by the treatment of **13** with small amount of NaOEt (0.1 eq.) in refluxing ethanol (yield 25.3%). Alkaline hydrolysis of **14** gave the corresponding carboxylic acid **15** in 60.3% yield, and **15** was again treated with ethyl oxalate to give 4-carboxy-2,3-dimethyl-5-ethoxalyl-2-cyclopentenone (16) in 59% yield from **15**. Treatment of **16** with formalin as usual afforded 4-carboxy-2,3-dimethyl-5-methylene-2-cyclopentenone (17), which was isolated from the bacterial broth that produced methylenomycin A (1).[5]

The epoxidation of **15** in basic hydrogen peroxide solution afforded the epoxide (18), which was converted into 4-carboxy-2,3-dimethyl-2,3-epoxy-5-ethoxalylcyclopentanone (19) by the reaction with ethyl oxalate. Treatment of **19** with formalin gave the expected compound **1**.

EXPERIMENTAL PROCEDURES

Infrared spectra were taken with a JASCO IRA-2 spectrometer. Mass spectra were measured with a Hitachi RMU-6MG instrument. Nuclear magnetic resonance spectra were recorded with a JNM MH-60 spectrometer.

2,3-Dimethyl-2-cyclopentenone (5). A mixture of cyclotene (28.3 g, 0.25 mol) and pyrrolidine (21.6 g, 0.3 mol) in 200 ml of benzene was refluxed under stirring using a Dean-Stark trap for 3 hr. After removal of the solvent, the residue was distilled *in vacuo* to afford 34.6 g (81.5%) of 2-pyrrolidino-5-methyl-2-cyclopentenone (**4**), bp 133~134°C/20 mm (lit.[6] bp 85~90°C/0.4 mm). This was used next step without further characterization owing to its instability.

To a stirred solution of Grignard reagent prepared from Mg (10.0 g, 0.42 mol) and CH_3I (60.0 g, 0.42 mol) in 100 ml of ether was added **4** (34.6 g, 0.21 mol) in 70 ml of ether dropwise at room temperature and the mixture was refluxed for 2 hr. After removal of the solvent, the residue was carefully treated with 150 ml of water and 150 ml of conc. HCl and the mixture was refluxed for 6 hr. The resulting mixture was saturated with NH_4Cl and extracted with three 100 ml portions of chloroform. The extract was washed with 5% NaOH, 3 N HCl, water and brine, and dried over Na_2SO_4. Distillation *in vacuo* gave 18.7 g of pure **5**, bp 75~77°C/20 mm (81% yield from cyclotene). IR ν_{max} cm^{-1}: 2920, 2850, 1690, 1640, 1440, 1330, 1300, 1185, 1070. NMR $\delta^{CCl_4}_{Me_4Si}$ ppm: 1.6 (3H, s), 2.05 (3H, s), 2.20~2.75 (4H, m). MS *m/z*: 110 (M^+), 95, 81, 79, 67, 58, 54.

2,3-Dimethyl-5-morpholinomethyl-2-cyclopentenone (6). A mixture of **5** (1.1 g, 0.01 mol), morpholine hydrochloride (1.23 g, 0.01 mol), few drops of conc. HCl and 1.5 g of paraformaldehyde in 15 ml of ethanol was refluxed for 4 hr. Evaporation of the solvent gave an oily residue, to which was added 10 ml of water and it was extracted with three 10 ml portions of ether to remove unreacted **5**. The aqueous solution was made basic with 1 g of sodium carbonate and extracted three 10 ml portions of ether. The ether extract was washed with water, saturated NH_4Cl solution and dried over Na_2SO_4, Removal of the solvent gave 0.9 g of crude **6**, which was further purified by silica-gel column chromatography (ether–ethanol=95:5) to afford 0.7 g of pure **6** (yield 33%). IR ν_{max} cm^{-1}: 2900, 2800, 1640, 1420, 1380, 1320, 1260, 1108, 1010, 910, 860, 780. NMR $\delta^{CCl_4}_{Me_4Si}$ ppm: 1.6 (3H, s), 2.02 (3H, s), 2.13~2.75 (9H, m), 3.55 (4H, t, J=4.5 Hz). MS *m/z*: 209 (M^+), 179, 166, 123, 110, 108, 101, 99, 86.

2,3-Dimethyl-5-methylene-2-cyclopentenone (3).

i) via 2,3-dimethyl-5-morpholinomethyl-2-cyclopentenone (6). A mixture of **6** (209 mg, 1 mmol) and CH_3I (1.4 g, 10 mmol) in 5 ml of methanol was stirred at room temperature for 20 hr. Removal of the solvent and excess CH_3I, the residue was poured into a mixture of 5 ml of 5% $NaHCO_3$ solution and 10 ml of CH_2Cl_2, and stirred at room temperature for 2 hr. The aqueous layer was separated and extracted with 10 ml of CH_2Cl_2. The combined organic layer was washed with water, brine, and dried over Na_2SO_4. Evaporation of the solvent gave 100 mg of **3** as a yellow oil which was purified by silica-gel

column chromatography to give 70 mg of pure **3**[2] (yield 57.4%). IR ν_{max} cm^{-1}: 2900, 1620, 1380, 1330, 1270, 1030, 930, 800. NMR $\delta^{CCl_4}_{Me_4Si}$ ppm: 1.72 (3H, s), 2.02 (3H, s), 2.95 (2H, s), 5.13 (1H, s), 5.80 (1H, s). MS *m/z*: 122 (M^+), 107, 94, 93, 91, 79, 77.

ii) via sodio derivative of 2,3-dimethyl-5-formyl-2-cyclopentenone (7a). To a stirred suspension of NaH (120 mg, 5 mmol) in 20 ml of ether was added the mixture of **5** (440 mg, 4 mmol) and ethyl formate (600 mg, 8 mmol), and then a few drops of ethanol successively. The resulted mixture was stirred for 8 hr at room temperature to afford sodio derivative of **7a**. To this sodio derivative (580 mg, 3.6 mmol) was added 10 ml of THF–DMSO (1 : 1) and 1.5 g of paraformaldehyde and the mixture was stirred for 20 hr. The resulting mixture was treated with water (10 ml) and the organic layer was separated and concentrated *in vacuo* to give an amber oil. This was redissolved in 20 ml of ether and washed with water and brine, and dried over Na_2SO_4. Removal of the solvent gave 0.3 g of **3** as a yellow oil (yield 47%).

iii) via sodio derivative of 2,3-dimethyl-5-ethoxalyl-2-cyclopentenone (7b). To a strirred suspension of NaH (100 mg, 4.2 mmol) in 20 ml of ether, was added the mixture of **5** (385 mg, 3.5 mmol) and ethyl oxalate (774 mg, 5.3 mmol), followed by the addition of a few drops of ethanol and the resulted mixture was stirred at room temperature for 8 hr. To the resulted sodio derivative of **7b** (700 mg, 3 mmol), was added 20 ml of THF, followed by the addition of K_2CO_3 (1.2 g, 9 mmol) in 2 ml of water and 2.5 ml of 37% formalin (30 mmol), and the mixture was stirred at 0 ~ 5°C for 2 hr. Usual work up gave 0.2 g of **3** (yield 54%).

2,3-Dimethyl-2,3-epoxycyclopentanone (8). To a stirred solution of **5** (2.2 g, 20 mmol) and 30% H_2O_2 (7.2 ml, 74 mmol) in 70 ml of methanol, was added 3 N NaOH (3.2 ml, 9.6 mmol) dropwise at 0°C, and then the mixture was stood in refrigerator for 22 hr. The excess H_2O_2 was decomposed with activated MnO_2 under cooling in an ice bath. The excess inorganic salts was filtered, and the filtrate was treated with 100 ml of saturated NH_4Cl solution and the mixture was extracted with three 100 ml portions of ether. The extract was concentrated *in vacuo* to give an oil, which was purified by silica-gel column chromatography (ether–hexane = 1 : 1) to afford 1.2 g of **8**[2] (yield 48%). IR ν_{max} cm^{-1}: 2900, 1730, 1440, 1400, 1380, 1320, 1200, 1060, 870, 780. NMR $\delta^{CCl_4}_{Me_4Si}$ ppm: 1.26 (3H, s), 1.46 (3H, s), 2.0 ~ 2.66 (4H, m). MS *m/z*: 126 (M^+), 97, 85, 69, 58.

2,3-Dimethyl-2,3-epoxy-5-methylenecyclopentanone (2). To a stirred suspension of NaH (115 mg, 4.8 mmol) in 20 ml of THF was added the mixture of **8** (504 mg, 4 mmol) and ethyl oxalate (876 mg, 6 mmol), followed by the addition of a few drops of ethanol and the resulted mixture was stirred at room temperature for 6 hr. To the resulted sodio derivative of **9** (990 mg, 4 mmol) was added 20 ml of THF, K_2CO_3 (2 g, 14.4 mmol) in 2 ml of water and 37% formalin (4 ml, 48 mmol), and the mixture was stirred at 0 ~ 5°C for 3 hr. Usual work up gave 0.5 g of crude **2**, which was further purified by silica-gel column chromatography (ether–hexane = 3 : 7) to afford 0.3 g of pure **2**[2] (yield 54%). IR ν_{max} cm^{-1}: 2900, 1720, 1640, 1400, 1301, 1020, 940, 850, 770. NMR $\delta^{CCl_4}_{Me_4Si}$ ppm: 1.43 (3H, s), 1.52 (3H, s), 2.75 (2H, dt, J = 2.0, J = 3.0 and J = 7.5 Hz), 5.29 (1H, t, J = 2.0 Hz), 6.03 (1H, t, J = 3.0 Hz). MS *m/z*: 138 (M^+), 123, 109, 95, 67, 43.

2,3-Dimethyl-2,3-epoxy-5-methylcyclopentanone (10). A mixture of **2** (200 mg, 1.45 mmol) in 10 ml of acetone was hydrogenated over 5% palladium on carbon. After removal of the catalyst and solvent, the residue was purified by silica-gel column chromatography (ether–hexane = 1 : 2) to give 150 mg of **10** as colorless oil. IR ν_{max} cm^{-1}: 2920, 1730, 1440, 1375, 1122, 1102, 1075, 992, 857. NMR $\delta^{CCl_4}_{Me_4Si}$ ppm: 1.07 (3H, d, J = 6.0 Hz), 1.23 (3H, s), 1.37 (3H, s), 1.87 ~ 2.25 (3H, m). MS *m/z*: 140 (M^+), 98, 85, 69, 58.

2,3-Dimethyl-5-methyl-2-cyclopentenone (11). To a cold solution of **3** (200 mg, 1.6 mmol) in 10 ml of ethanol was added 200 mg of $NaBH_4$ and the mixture was stirred for 3 hr at 0°C. To the resulted mixture was added 20 ml of saturated NH_4Cl and extracted with three 20 ml portions of ether. The extract was washed with saturated NH_4Cl and dried over Na_2SO_4. Evaporation of the solvent, the residue was redissolved in 10 ml of benzene and MnO_2 (1 g) was added portionwise to the stirred solution at room temperature. After removal of the solvent and excess MnO_2, the residue was purified by silica-gel column chromatography (ether–hexane = 1 : 1) to give 100 mg of **11**. IR ν_{max} cm^{-1}: 2870, 1680, 1640, 1435, 1380, 1320, 1040. NMR $\delta^{CCl_4}_{Me_4Si}$ ppm: 1.12 (3H, d, J = 6.8 Hz), 1.62 (3H, s), 2.00 (6H, s). MS *m/z*: 124 (M^+), 109, 81, 79, 67, 58.

2-Methylenecyclopentenone (12). To a solution of NaOEt prepared from Na (1.15 g, 0.05 mol) and 50 ml of ethanol was added the mixture of cyclopentanone (4.2 g, 0.05 mol) and ethyl oxalate (7.3 g, 0.05 mol), and the resulted mixture was stirred for 3 hr at 5°C. Sodium salt of α-ethoxalyl cyclopentanone was precipitated from the reaction mixture almost quantitatively (yield 98%). To a suspension of sodium salt of α-ethoxalyl cyclopentanone (1 g, 5 mmol) in 15 ml of THF was added 37% formalin (4.5 ml, 0.05 mol) and the mixture was stirred at 0°C for 10 min. Usual work up gave 0.2 g of **12**.[8] IR ν_{max} cm^{-1}: 2900, 1720, 1635, 1400, 1250, 1080, 925. NMR $\delta^{CCl_4}_{Me_4Si}$ ppm: 1.85 ~ 2.37 (4H, m), 2.50 ~ 2.87 (2H, m), 5.20 (1H, s), 5.78 (1H, s). MS *m/z*: 96 (M^+), 68, 67, 58, 40.

Ethyl 2-acetyl-4-oxohexanoate (13). A mixture of sodium salt of ethyl acetoacetate in 70 ml of THF prepared from Na (3.2 g, 0.14 mol) and ethyl acetoacetate (18.2 g, 0.14 mol) and 1-bromo-2-butanone[7] (18.6 g, 0.12

mol) was stirred for 8 hr at room temperature. Evaporation of the solvent gave an oily residue, to which was added 30 ml of water and it was extracted with two 50 ml portions of ether. The extract was washed with water and brine, and dried over Na_2SO_4. Distillation *in vacuo* gave 19.8 g of **13**, bp 116~120°C/1.5 mm (lit.[4] bp 85~87°C/0.3 mm), (yield 82.8%). IR ν_{max} cm^{-1}: 2950, 1730, 1700, 1460, 1415, 1380, 1260, 1150, 1120, 1020, 850. NMR $\delta^{CCl_4}_{Me_4Si}$ ppm: 0.98 (3H, t, J=7.5 Hz), 1.23 (3H, t, J=6.8 Hz), 2.21 (3H, s), 2.30~2.86 (4H, m), 2.75~4.73 (3H, m). MS *m/z*: 200 (M^+), 171, 158, 143, 140, 129, 113, 101.

4-Carbethoxy-2,3-dimethyl-2-cyclopentenone (14). A stirred mixture of NaOEt prepared from NaH (120 mg, 5 mmol) and 250 ml of ethanol, and **13** (10 g, 50 mmol) was refluxed for 5 hr. The reaction mixture was neutralized with 5 ml of 1 N HCl and the solvent was removed *in vacuo* to give a yellow oil, to which was added 20 ml of water and it was extracted with three 30 ml portions of ether. The extract was washed with water and brine, and dried over Na_2SO_4. Distillation *in vacuo* gave 4.9 g of ethyl 4-oxohexanoate (bp 84~85°C/4 mm) and 2.3 g of **14**, bp 113~115°C/4 mm (lit.[4] bp 83~84°C/0.2 mm) (yield 25.3%). IR ν_{max} cm^{-1}: 2950, 1700, 1640, 1430, 1380, 1320, 1250, 1190, 1160, 1070, 1035, 860. NMR $\delta^{CCl_4}_{Me_4Si}$ ppm: 1.23 (3H, t, J=6.8 Hz), 1.65 (3H, s), 2.00 (3H, s), 2.38 (2H, d, J=5.3 Hz), 3.30~3.55 (1H, bs), 4.07 (2H, q, J=6.8 Hz). MS *m/z*: 182 (M^+), 171, 158, 143, 136, 109.

4-Carboxy-2,3-dimethyl-2-cyclopentenone (15). To a suspension of **14** (1.8 g, 0.01 mol) in 10 ml of water was added 10 N NaOH (total 3 ml) dropwise keeping pH of 12 until clear solution was obtained. The mixture was extracted with 20 ml of ether to remove unreacted **14**, and the aqueous layer was acidified with 3 N HCl (12 ml) and extracted with three 20 ml portions of ether. The extract was washed with water and brine, and dried over Na_2SO_4. Removal of the solvent gave 1.5 g of crude **15**. Recrystallization from ether–hexane (1 : 2) afforded 1.0 g of pure **15** (yield 60.3%), mp 80~82°C (lit.[4] mp 81~83°C). IR ν^{KBr}_{max} cm^{-1}: 3450, 2950, 1720, 1670, 1630, 1390, 1330, 1310, 1230, 1180, 1090, 940, 900. NMR $\delta^{CDCl_3}_{Me_4Si}$ ppm: 1.75 (3H, s), 2.10 (3H, s), 2.56 (2H, d, J=4.5 Hz), 3.43~3.80 (1H, m), 10.98 (1H, s). MS *m/z*: 166 (M^+), 151, 138, 121, 108, 93, 91, 79, 77.

4-Carboxy-2,3-dimethyl-5-ethoxalyl-2-cyclopentenone (16). To a cold suspension of NaH (105.6 mg, 4.4 mmol) in 5 ml of THF was added the mixture of **15** (308 mg, 2 mmol) and ethyl oxalate (876 mg, 6 mmol) in 8 ml of THF at 0°C. The reaction was initiated with a few drops of ethanol under ice-cold temperature and allowed to react at room temperatrue for 3 hr. Removal of the solvent, 10 ml of water was added to the residue and extracted with three 10 ml portions of ether to remove excess ethyl oxalate. The aqueous layer was acidified with 5 ml of 3 N HCl and extracted with three 10 ml portions of ethyl acetate. Evaporation of the solvent gave 0.6 g of crude **16**, which was purified by column chromatography (silica-gel impregnated with 0.5% H_3PO_4, ether–hexane = 5 : 1) to afford 300 mg of pure **16** as a yellow oil. IR ν_{max} cm^{-1}: 3450, 2950, 1720, 1660, 1380, 1310, 1240, 1200, 1100, 1080, 1010, 820, 780. NMR $\delta^{CDCl_3}_{Me_4Si}$ ppm: 1.35 (3H, t, J=7.5 Hz), 1.85 (3H, s), 2.18 (3H, s), 4.35 (2H, q, J=7.5 Hz), 4.40 (1H, s), 10.75 (2H, bs).

4-Carboxy-2,3-dimethyl-5-methylene-2-cyclopentenone (17). A mixture of **16** (100 mg, 0.4 mmol) in 5 ml of THF, K_2CO_3 (165.6 mg, 1.2 mmol) in 2 ml of water and 37% formalin (0.3 ml, 4 mmol) was stirred for 2 hr at 0~5°C. To the resulting mixture was added 10 ml of water and it was extracted with three 10 ml portions of ether. The extract was washed with water and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by preparative TLC (silica-gel impregnated with 0.2% H_3PO_4, ether–hexane = 5 : 1) to afford 50 mg of **17**,[5] mp 93~95°C. IR ν^{KBr}_{max} cm^{-1}: 3450, 2900, 1690, 1620, 1390, 1330, 1250, 1190, 1020, 950, 800. NMR $\delta^{CCl_4}_{Me_4Si}$ ppm: 1.85 (3H, s), 2.35 (3H, s), 4.05~4.15 (1H, bs), 5.64 (1H, d, J=1.0 Hz), 6.20 (1H, d, J=1.5 Hz), 8.30 (1H, s). MS *m/z*: 166 (M^+), 121, 93, 91, 79, 77.

4-Carboxy-2,3-dimethyl-2,3-epoxycyclopentanone (18). To a cold mixture of **15** (616 mg, 4 mmol) and 15% H_2O_2 (8 ml, 40 mmol) was added K_2CO_3 (552 mg, 4 mmol) in 1 ml of water and the mixture was stood in refrigerator for 24 hr. The excess H_2O_2 was decomposed with MnO_2 under cooling in an ice bath. The inorganic salt was filtered, and the filtrate was acidified with a few drops of 6 N HCl and extracted with three 20 ml portions of ethyl acetate. Removal of the solvent gave 600 mg of crude **18**, which was purified by preparative TLC (silica-gel impregnated with 0.2% H_3PO_4, ether–hexane = 3 : 1) to give 510 mg of **18**, mp 120~122°C (lit.[4] mp 125.5~127°C). IR ν^{KBr}_{max} cm^{-1}: 3400, 2920, 1740, 1705, 1440, 1380, 1340, 1310, 1275, 1235, 1190, 1105, 1095, 1065, 950, 810. NMR $\delta^{CDCl_3}_{Me_4Si}$ ppm: 1.37 (3H, s), 1.55 (3H, s), 2.20 (1H, dd, J=18 and J=2.0 Hz), 2.56 (1H, dd, J=18 and J=7.5 Hz), 3.32 (1H, dd, J=7.5 and J=2.0 Hz), 9.63 (1H, s). MS *m/z*: 170 (M^+), 125, 99, 97, 85, 83, 44.

4-Carboxy-2,3-dimethyl-2,3-epoxy-5-ethoxyalylcyclopentanone (19). To a cold suspension of NaH (158.4 mg, 3 mmol) in 10 ml of THF was added the mixture of **18** (510 mg, 3 mmol) and ethyl oxalate (876 mg, 6 mmol) in 10 ml of THF at 0°C. The reaction was initiated with a few drops of ethanol and continued for 10 hr at 0~5°C. After removal of the solvent, 10 ml of water was added to the residue and it was extracted with three 10 ml portions of ether to remove excess ethyl oxalate. The aqueous layer was acidified with 4 ml of 3 N HCl and extracted with three 10 ml portions of ethyl acetate. Evaporation of the solvent gave 0.5 g of crude **19**, which was purified by preparative

TLC (silica-gel impregnated with 0.2% H_3PO_4, ether–hexane = 3 : 1) to give 0.2 g of **19** as a yellow oil. IR ν_{max} cm^{-1}: 3400, 2950, 1730, 1680, 1440, 1380, 1300, 1240, 1200, 1105, 1080, 1020, 870, 760. NMR $\delta^{CDCl_3}_{Me_4Si}$ ppm: 1.33 (3H, t, J=6.8 Hz), 1.50 (3H, s), 1.57 (3H, s), 4.12~4.47 (4H, m), 10.72 (1H, bs).

Methylenomycin A (1). A mixture of **19** (108 mg, 0.4 mmol) in 5 ml of THF, K_2CO_3 (220 mg, 1.6 mmol) in 1 ml of water and 37% formalin (0.3 ml, 4 mmol) was stirred for 30 min at 0~5°C and then 1 hr at room temperature. To the reaction mixture was added 10 ml of brine and it was extracted with three 20 ml portions of ether. The extract was washed with brine and dried over Na_2SO_4. Removal of the solvent gave 30 mg of **1**, mp 113~115°C (lit.[4] mp 115~117°C). IR ν^{KBr}_{max} cm^{-1}: 3500, 2950, 1730, 1640, 1440, 1395, 1310, 1250, 1200, 1105, 1020, 959, 910, 890, 740. NMR $\delta^{CDCl_3}_{Me_4Si}$ ppm: 1.48 (3H, s), 3.82 (1H, m), 5.65 (1H, d, J=1.5 Hz), 6.27 (1H, d, J=2.3 Hz), 9.33 (1H, bs). MS m/z: 182 (M^+), 167, 137, 124, 109, 95, 67.

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