BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 1144—1147 (1972)

Synthesis of 5,5-Dimethyl-4-acetoxy-2-cyclopentenone, an Intermediate in the Total Synthesis of Illudin M, through Sulfur Compounds. A Novel Intramolecular Migration of Ethylenedioxy Group

Takeshi MATSUMOTO, Haruhisa SHIRAHAMA, Akitami ICHIHARA, Hyonsobb SHIN, and Shohei KAGAWA

Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo

(Received August 6, 1971)

5,5-Dimethyl-4-acetoxy-2-cyclopentenone, an intermediate in the total synthesis of illudin M, has been prepared from 1-methylsulfinyl-3,3-dimethyl-4,4-ethylenedioxy-2-pentanone as well as from 1,1-trimethylenedithio-3,3-dimethyl-4,4-ethylenedioxy-2-pentanone. An example of new intramolecular transketalization has been described.

A report was given on a total synthesis[1] of *dl*-illudin M. The synthesis was started from the Michael addition of a sulfoxide **1** to a cyclopentenone **2**. In the early stage[2] of this work, it was thought to be of interest to convert a sulfoxide **5** or a dithiane **10**, both similar in structure to **1**, into the cyclopentenone **2**.[3] If the conversion were possible, it would mean that illudin M can be synthesized from two structurally similar seven-carbon units.

The present paper describes the synthesis of the cyclopentenone **2** along this line.[4,5] At first, the carbonyl group of ethyl dimethylacetoacetate (**3**)[6] was masked with ethylene glycol in the usual manner (52% yield), and the ketal ester was treated with methylsulfinyl carbanion according to Corey's method[7]

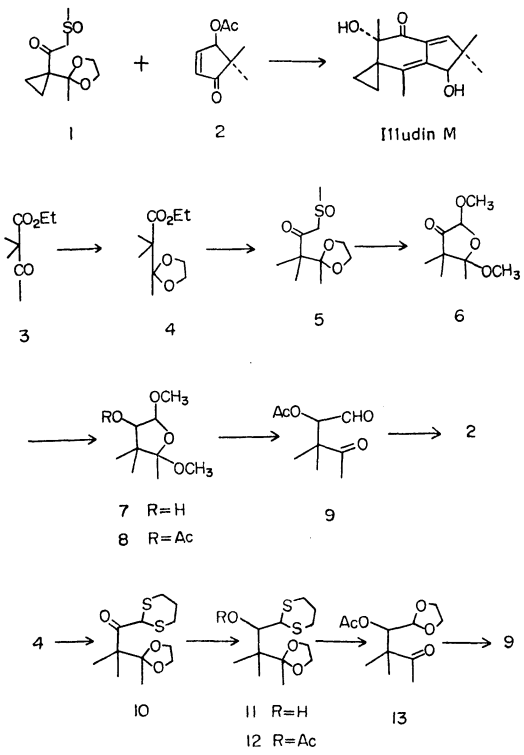


Fig. 1.

1) T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, S. Matsumoto, and S. Nishida, *J. Amer. Chem. Soc.*, **90**, 3280 (1968).

2) T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, N. Ito, T. Hisamitsu, T. Kamada, and F. Sakan, *Tetrahedron Lett.*, **1967**, 4097.

3) T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, N. Ito, T. Hisamitsu, T. Kamada, K. Saito, S. Nishida, and S. Matsumoto, *icid.*, **1968**, 1925.

4) A part of the present paper was presented in the preliminary report.[1]

5) An alternative route: See T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, S. Nishida, S. Matsumoto, K. Saito and H. Hashimoto, This Bulletin, **45**, 1140 (1972).

6) K. Folkers and H. Adkins, *J. Amer. Chem. Soc.*, **53**, 1416 (1931).

7) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965).

to give a β-ketosulfoxide **5**, mp 53—56°C, in 91% yield. It has been shown that in general β-ketosulfoxides gave α-ketoacetals on treatment with iodine in methanol.[8] Compound **5** was accordingly treated under these conditions to afford a mixture of an epimeric pair of tetrahydrofuranones **6** in moderate yield and minor products. By chromatography on silica gel the mixture was separated into four fractions. The first fraction obtained in a small amount as an oil was found to be a mixture of an epimeric pair of 2,3,3-trimethyl-2-methoxy-5-methylthiotetrahydro-4-furanone, on the basis of the NMR spectrum. The second and third fractions contained the main products of the reaction. NMR spectra indicated that each product was one of the epimeric pair of 2,3,3-trimethyl-2,5-dimethoxytetrahydro-4-furanone (**6**). The last fraction was a mixture of epimers of **6** and unidentified substances. Reduction followed by acetylation of each epimer of **6** afforded a single, but not identical, product: diastereoisomeric 2,3,3-trimethyl-2,5-dimethoxy-4-acetoxytetrahydrofuran (**8**), respectively. Both isomers of **8** gave the same compound, 2-acetoxy-3,3-dimethyl-4-ketopentanal (**9**, bis DNP mp 201—202°C) in moderate yield, on being dissolved in a mixture of 1 N hydrochloric acid and tetrahydrofuran (1/1). For the preparation of the final product, cyclopentenone **2**, the series of reactions (**5**→**9**) can be performed without purification of the intermediates. A crude product containing **9** was obtained in 47.5% yield from **5**. Vpc analysis revealed that one third of the product was the desired aldehyde **9**. The crude aldehyde **9** was cyclized to afford 5,5-dimethyl-4-acetoxy-2-cyclopentenone (**2**)[3] in 21% yield based on the crude product, on treatment with sodium hydride in a large amount of benzene under refluxing.

Pure aldehyde **9** was also obtained through a 1,3-dithiane derivative as follows. The addition reaction of an anion of 1,3-dithiane[9] to dimethylacetoacetic ester afforded 1,1-trimethylenedithio-3,3-dimethyl-4,4-ethylenedioxy-2-pentanone (**10**), mp 89—90°C. Reduction and acetylation of the dithiane **10** gave 1,1-trimethylenedithio-2-acetoxy-3,3-dimethyl-4,4-ethylenedioxypentane (**12**) which was treated with mercuric chloride and cadmium carbonate in aqueous acetone in order to remove the trimethylenedithio group.[10]

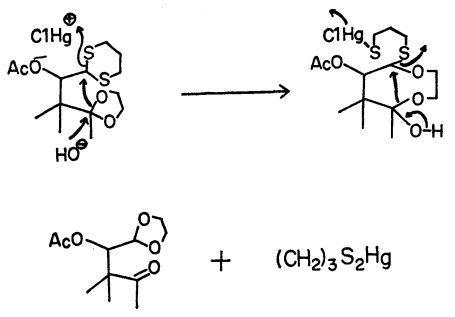
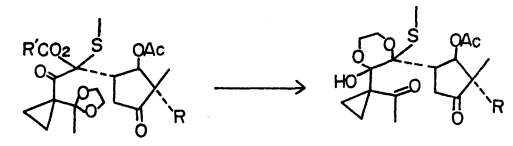


Fig. 2.



14 R=CH_3, R'=CH_3
15 R=CH_2OAc, R'=CH_3
16 R=CH_2OAc, R'=CH_2OCH_3

17 R=CH_3
18 R=CH_2OAc

Fig. 3.

The compound obtained lacked sulfur atom, but it was not the expected aldehyde and instead a ketone. The NMR spectrum showed signals for a *gem*-dimethyl group as singlets at τ 8.96 and 8.76, two acetyl groups as singlets at τ 7.89 and 7.81, an ethylenedioxy group as a rather sharp (W1/2=6Hz) multiplet at τ 6.31 and two methine groups as an AB quartet at τ 5.06 and 4.82 (J=7 Hz). Ethylenedioxy group was undoubtedly transferred to the γ-carbonyl group on the basis of the NMR spectrum and the structure of the product was expressed as 1,1-ethylenedioxy-2-acetoxy-3,3-dimethylpentanone (**13**). The reaction may be rationalized by a transition state containing as eight membered ring (Fig. 2). Similar rearrangements of ethylenedioxy group have been observed in our synthetic studies on illudin M[1] and S.[11,12] Methyl ketone **13** was readily converted into aldehyde **9** by a similar treatment to that for the deacetalization of **8**.

Experimental

Ethyl 2,2-dimethyl-3-ethylenedioxybutyrate (4). Ethyl 2,2-dimethyl-3-ketobutyrate (**3**)[6] was dissolved in 300 m*l* of benzene containing 27 g of ethylene glycol and 200 mg of *p*-toluenesulfonic acid. The mixture was heated at the reflux temperature of benzene. The water formed was removed by azeotropic distillation with a Dean-Stark separator and heating was continued until 4 m*l* of water was removed. The reaction mixture was washed three times with aqueous sodium carbonate and three times with water and dried. The solvent was removed and the residue was distilled to yield 27.2 g (52%) of **4**: bp 110°C/17 mmHg; IR (neat) 1730 cm^{-1} (CO); NMR τ ($CDCl_3$) 8.71 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 8.80 (6H, s, 2×CH_3), 8.68 (3H, s, CH_3), 6.10 (4H, s, OCH_2CH_2O), 5.88 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$).

1-Methylsulfinyl-3,3-dimethyl-4,4-ethylenedioxy-2-pentanone (5). The compound was prepared by the general method for preparation of β-ketosulfoxides according to Corey and Chaykovsky.[7] Ester **4** (27.2 g) was added dropwise to a dimethyl sulfoxide solution of methylsulfinyl carbanion prepared from 140 m*l* of dimethyl sulfoxide and 12.9 g of sodium hydride (50% mineral oil dispersion) under ice-water cooling and mechanical stirring in the atmosphere of nitrogen. The ice-water bath was removed, stirring was continued for 2 hr at room temperature and the reaction mixture was

8) T. L. Moore, *J. Org. Chem.*, **32**, 2786 (1967).
9) E. J. Corey and D. Seebach, *Angew. Chem.*, **77**, 1135 (1965).
10) A. G. Brook, J. M. Duff, P. F. Jones, and N. R. Davis, *J. Amer. Chem. Soc.*, **89**, 431 (1967).
11) T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, and K. Miyano, *Tetrahedron Lett.*, **1971**, 2049.
12) In the course of studies on total synthesis of illudins,[1,11] reactions such as **14**→**17** and **16**→**18** (Fig. 3) were found. Warming compounds **14** and **16** in ethanol was enough to cause the transfer of the ethylenedioxy group but the rearrangement (**15**→**18**) did not occur under the same conditions.

then poured into 500 ml of water, wshed three times with benzenee, neutralized with dilute acetic acid to pH of 5—6 (pH paper), and extracted three times with chloroform. The combined extracts were washed three times with a saturated salt solution and dried over anhydrous sodium sulfate, and evaporated to yield 28.7 g (91%) of the ketosulfoxide **5** as a yellow crystalline solid. A small sample was recrystallized from carbon tetrachloride for analysis: mp 53—56°C; IR (nujol) 1700 cm^{-1}; NMR τ ($CDCl_3$) 8.77 (3H, s, $CH_3C\langle^{O}_{O}$), 8.75 (6H, s, CH_3CCH_3), 7.27 (3H, s, $SOCH_3$), 5.99 (4H, s, OCH_2CH_2O), 5.99 and 5.57 (2H, ABq, J=16 Hz, $SOCH_2CO$).

Found: C, 51.15; H, 7.65%. Calcd for $C_{10}H_{18}O_4S$: C, 51.27; H, 7.75%.

*2,3,3-Trimethyl-2,5-dimethoxytetrahydro-4-furanone (**6**).* Keto sulfoxide **3** (6.3 g) was dissolved in 120 ml of methanol containing 3.44 g of iodine. The solution was refluxed for 4 hr, and then allowed to cool. Most of the methanol was removed at room temperature on a rotary evaporator under reduced pressure. The dark residual oil was taken up in chloroform and washed twice with saturated sodium thiosulfate solution. The light yellow chloroform solution was dried with anhydrous sodium sulfate and the solvent was removed under reduced pressure. The residual oil was chromatographed on silica gel with benzene as a solvent and separated into four fractions.

The first fraction was 81 mg of an oil: IR (neat) 1765 cm^{-1}; NMR τ ($CDCl_3$) 8.90 (6H, s, CH_3CCH_3), 8.58 (3H, s, CH_3), 7.72 and 7.70 (3H, twin s, SCH_3), The qualitative analysis for sulfur was positive and the oil was converted into **6** by treatment with iodine in methanol. Thus, the oil should be a mixture of an epimeric pair of 2,3,3-tri methyl-2-methoxy-5-methylthiotetrahydro-4-furanone. The second fraction (877 mg): IR (neat) 1780 cm^{-1}; NMR ($CDCl_3$) 8.91, 8.86 and 8.57 (each 3H, s, 3×CH_3), 6.67 and 6.42 (each 3H, s, 2×OCH_3), 5.36 (1H, s, OCHO). The third fraction (1.338 g): IR 1780 cm^{-1}; NMR τ ($CDCl_3$) 8.90 (6H, s, CH_3CCH_3), 8.60 (3H, s, CH_3), 6.68 and 6.42 (each 3H, s, 2×OCH_3), 5.04 (1H, s, -OCHO-). From these spectral data, it was deduced that each of the second and the third fractions contained an epimer of **6**. The fourth fraction (694 mg) was a mixture of **6** and unidentified substances.

*2,3,3-Trimethyl-2,5-dimethoxy-4-acetoxytetrahydrofuran (**8**).* Each epimer of furanone **6** was separately reduced with sodium borohydride and then acetylated with acetic anhydride and pyridine. The earlier eluted furanone **6** (877 mg) gave 609 mg of a single epimer of **8**: IR (neat) 1750, 1240 cm^{-1}; NMR τ (CCl_4) 9.00 (6H, s, CH_3CCH_3), 8.78 (3H, s, CH_3), 7.95 (3H, s, OAc), 6.80 and 6.68 (each 3H, s, OCH_3), 5.29 and 5.11 (2H, ABq, J=6 Hz, $AcOCHCH\langle^{O}_{O}$). The later eluted furanone **6** (40 mg) gave 23 mg of another epimer of **8**: IR (neat) 1740, 1240 cm^{-1}; NMR τ (CCl_4) 9.04, 8.98 and 8.82 (each 3H, s, CH_3), 7.92 (3H, s, OAc), 6.78 and 6.55 (each 3H, s, OCH_3), 5.24 and 5.01 (2H, ABq, J=6 Hz, $AcOCHCH\langle^{O}_{O}$).

*2-Acetoxy-3,3-dimethyl-4-ketopentanal (**9**).* Each epimer of **8** was separately converted into aldehyde **9**. A sample of acetoxyfuran was dissolved in about 20 times its volume of a mixture of 1 N hydrochloric acid and tetrahydrofuran and allowed to stand for 3 hr at room temperature. The reaction mixture was extracted with chloroform three times. The combined extracts were washed with water twice, dried and evaporated to leave aldehyde **9**. IR (neat) 1740, 1705, 1230 cm^{-1}; NMR τ (CCl_4), 8.75 (6H, s, CH_3CCH_3), 7.86 (6H, s, OAc and $COCH_3$), 5.06 (1H, s, AcOCH), 0.50 (1H, s, CHO). Bisdinitrophenylhydrazone: mp 201—202°C.

Found: C, 46.21; H, 4.20; N, 20.19%. Calcd for $C_{21}H_{22}N_8O_{10}$: C, 46.15; H, 4.06; N, 20.50%.

Crude aldehyde **9** can be prepared from sulfoxide **5** without purification throughout the process as follows. Treatment of 8.2 g of the sulfoxide **5** gave 4.5 g of a crude epimeric mixture of acetoxyfuran **8**, 2.4 g which was hydrolysed to give 1.65 g of a crude product. Gas chromatographic analysis revealed that one third of the product was the desired aldehyde **9**.

*5,5-Dimethyl-4-acetoxy-2-cyclopentenone (**2**).* The above crude product (800 mg) containing aldehyde **9** was refluxed under stirring with 300 mg of sodium hydride in 400 ml of benzene for 9 hr. The reaction mixture was filtered and the solvent was removed. The resulting oil was fractionated by preparative gas chromatography on DEGS column (3m, at 270°C, He: 100 ml/min, reteniton time: 10 min) to give 150 mg of the cyclopentenone. The IR spectrum was identical with that of the authentic sample.[2]

*1,1-Trimethylenedithio-3,3-dimethyl-4,4-ethylenedioxy-2-pentanone (**10**).* A solution of 11.7 g of *n*-butyl bromide in 15 ml of ether was added dropwise to 1.4 g of lithium covered with 35 ml of ether −30——40°C and the mixture was stirred for 1.5 hr at 0—10°C. The resulting solution was added dropwise to a stirred solution of 3 g of 1,3-dithian in 50 ml of tetrahydrofuran at −30——40°C. To the solution prepared above was added dropwise 5 g of ethyl dimethylacetoacetate ethylene ketal (**4**) at −20——30°C with stirring. The reaction mixture was allowed to stand at the same temperature range for 40 hr and then poured into water. The solution was acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with a saturated salt solution and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was distilled to give 2 g (29.3%) of **10**, bp 152—152.5°C/4 mmHg, which crystallized soon and was recrystallized from isopropyl ether: mp 89—90°C; IR (nujol) 1690 cm^{-1}; NMR τ (CCl_4) 8.74 (9H, s, 3×CH_3), 8.0—7.4 and 6.8—6.2 (4H and 2H, m, $S(CH_2)_3S$), 6.01 (4H, s, OCH_2CH_2O), 5.30 (1H, s, SCHS).

Found: C, 52.07; H, 7.05%. Calcd for $C_{12}H_{20}O_3S_2$: C, 52.16; H, 7.30%.

*1,1-Trimethylenedithio-3,3-dimethyl-4,4-ethylenedioxy-2-pentanol (**11**).* Ketone **10** (1.375 g) was dissolved in anhydrous ether and 50 mg of lithium aluminum hydride was added. After standing overnight, another 50 mg of lithium aluminum hydride was added and the reaction mixture was refluxed for 6 hr, poured on ice-water and the product was extracted with ether. The extract was dried and the solvent was removed to leave 1.24 g (90%) of **11**. Crystalline mass was recrystallized from isopropyl ether and analyzed, mp 68—69°C: IR (neat) 3450 cm^{-1}; NMR τ (CCl_4) 8.97, 8.87 and 8.71 (each 3H, s, CH_3), 8.5—6.5 (6H, m, $S(CH_2)_3S$), 6.02 (4H, s, OCH_2CH_2O), 6.10 (1H, d, J=3 Hz, HOCH), 5.80 (1H, d, J=3 Hz, SCHS).

Found: C, 51.81; H, 7.86%. Calcd for $C_{12}H_{22}O_3S_2$: C, 51.79; H, 7.97%.

Alcohol **11** was acetylated with acetic anhydride and pyridine in the usual manner to give acetate **12**: IR (neat) 1745, 1235 cm^{-1}: NMR τ (CCl_4) 8.98, 8.90 and 8.70 (each 3H, s, CH_3), 7.89 (3H, s, OAc), 6.03 (4H, s, OCH_2CH_2O), 5.32 (1H, d, J=2 Hz, SCHS), 4.85 (1H, d, J=2 Hz, AcOCH).

*1,1-Ethylenedioxy-2-acetoxy-3,3-dimethylpentanone (**13**).*

Acetate **12** (127 mg) was dissolved in 10 m*l* of acetone and 630 mg of mercuric chloride, 917 mg of cadmium carbonate and 90 mg of water were added and the whole solution was stirred for 6 hr at room temperature. The acetone was removed and the residue was extracted with chloroform. After evaporation of the solvent, the extracted mass was chromatographed on silica gel column employing a mixture of ethyl acetate and benzene (1 : 9) as a solvent to give 28 mg (31%) of **13**: IR (neat) 1750, 1710, 1230 cm^{-1}; NMR τ (CCl_4) 8.96 and 8.76 (each 3H, s, CH_3) 7.89 and 7.86 (each 3H, s, OAc and $COCH_3$), 6.13 (4H, m, W1/2= 6 Hz, OCH_2CH_2O), 5.06 and 4.82 (2H, ABq, J=7 Hz, $AcOCHCH\langle^{O}_{O}\rangle$).

Hydrolysis of ***13***. To a solution of 17 mg of ketoacetal **13** in 1 m*l* of tetrahydrofuran was added five drops of 6 N hydrochloric acid and the solution was left to stand overnight at room temperature. After addition of 1 m*l* of water, the solution was kept for a few minutes under reduced pressure to remove most of the tetrahydrofuran and the residue was extracted with chloroform three times. The combined extracts were washed with a saturated salt solution, dried and evaporated to leave 9 mg of an oil whose IR spectrum was identical with that of the aldehyde obtained from **8**.