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Synthesis and Conformation of Cyclopropane Intermediates in the Total Synthesis of Illudin M and S

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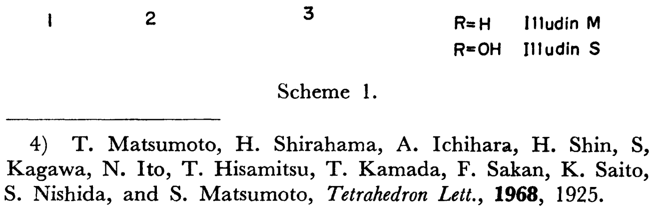
Several promising cyclopropane intermediates in the total synthesis of illudin M and S have been prepared. Survey of NMR of these compounds showed the conformation **17** to be unfavourable.

Preliminary reports were given on the total synthesis of illudin M and S[1,2]. Cyclopropyl ketone derivatives of general formula **1**, where X represents hydrogen or any groups activating methylene group, were desirable for the Michael reaction (Scheme 1) which was expected for combined cyclopropane and cyclopentane moieties to give useful intermediates **3** for illudins. This paper describes the synthesis of several cyclopropane derivatives **6**, **9**, **12**, **13**, **14**, and **15** of this type and their preferred conformation.[3] Ethyl 2,2-ethano-3-ketobutyrate (**4**), bp 90—102°C/20 mmHg, was prepared by the alkylation of acetoacetic ester with ethylene bromide in 24% yield and the carbonyl group of compound **4** was masked with ethylene glycol in the usual manner to give ketal **5**, bp 127—137°C/20 mmHg, in 68% yield. Ketal **5** was converted into 1-methanesulfinyl-3,3-ethano-4,4-ethylenedioxy-2-pentanone (**9**), mp 41—43°C in 91% yield by treatment with methylsulfinyl carbanion according to Corey's general procedure.[5] The Pummerer reaction of **9** by heating with acetic anhydride at reflux temperature for 3 hr afforded acetoxysulfide **12**, mp 44—46°C, in 79% yield. On treatment with amalgamated aluminum in aqueous ethanol at room temperature, the methylthio group of **12** and



Scheme 1.

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

[2] T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, and K. Miyano, *Tetrahedron Lett.*, **1971** 2049.

[3] Our purpose was finally achieved[4] by the Michael reaction of β-ketosulfoxide **9** (**1**, $X=SOCH_3$) with cyclopentenone **2**. Attempted Michael reactions of cyclopropyl ketones **6**, **12**, **13**, **14**, and **15** with **2** were unsuccessful.

[4] T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S, Kagawa, N. Ito, T. Hisamitsu, T. Kamada, F. Sakan, K. Saito, S. Nishida, and S. Matsumoto, *Tetrahedron Lett.*, **1968**, 1925.

[5] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

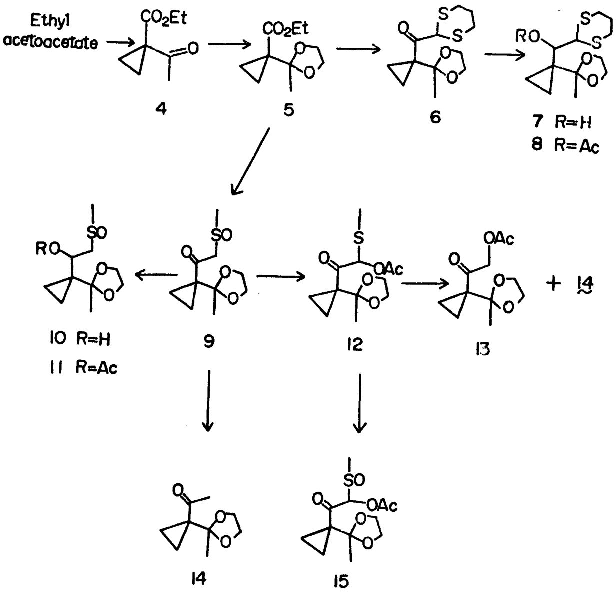


Fig. 1.

part of the acetoxy group were removed to give acetoxymethyl ketone **13**, bp 89—92°C/1 mmHg (30%) and methyl ketone **14**, bp 45—50°C/1 mmHg (25%). The latter was directly obtained by the treatment of **9** with the same reagent in aqueous tetrahydrofuran. Sulfide **12** was converted into sulfoxide **15** by oxidation with hydrogen peroxide in acetic acid (26%).

1,1-Trimethylenedithio-3,3-ethano-4,4-ethylenedioxy-2-pentanone (**6**), mp 59—60°C, was obtained by the action of an anion of 1,3-dithiane on the ester **5** according to Corey's method[6] in 45% yield.

We would like to add a note on the conformation of the cyclopropyl methyl ketone ethylene ketals. The long range shielding effect of the cyclopropane ring is well known[7,8] from which the instability of the conformation **16** of cyclopropyl methyl ketones has been deduced[7]. By comparison of chemical shifts of methyl group on the dioxolane rings with those of the compounds with *gem*-dimethyl group in the place of cyclopropane ring, information on the conformation of the above cyclopropyl methyl ketone ethylene ketals might be obtained. Three of such *gem*-dimethyl compounds (**21**, **18**, **22**) were prepared for another purpose[9] and some more pairs of cyclopropyl ketone ketals and the corresponding *gem*-dimethyl compounds were available. Cyclopropyl ketones **6** and **9** were reduced with sodium borohydride to give hydroxydithiane derivative **7** and hydroxysulfoxide **10**, mp 120—122°C, respectively. Both alcohol **7** and **10** were converted into acetates **8** and **11** in the usual manner. The *gem*-dimethyl compounds corresponding to **10** and **11**, 1-methanesulfinyl-3,3-dimethyl-4,4-ethylenedioxy-2-pentanol (**19**) and its acetate **20**, were prepared from dimethylmethanesulfinylpentanone **18** in the same manner as in the preparation of **10** and **11**.

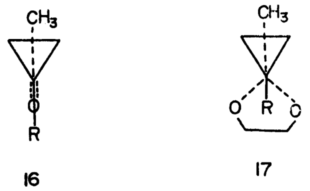
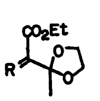
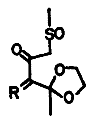
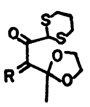
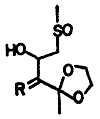
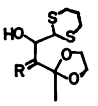
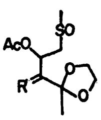
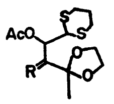


Fig. 2. Unstable conformations of cyclopropyl methyl ketones and their ketals.

As shown in Table 1, the methyl signals of the cyclopropyl compounds invariably appeared at a lower field than those of the *gem*-dimethyl compounds, showing that conformation **17** of the cyclopropyl compounds is not preferable. The fact that conformation **17** in which the methyl group situated just above the cyclopropane ring is unfavorable can be explained by the repulsion between cyclopropane ring and eclipsed methyl group. Instability of the so called transoid cyclopropyl methyl ketones **16** might be due, at least in part, to the same effect.

TABLE 1. CHEMICAL SHIFTS (τ) OF METHYL GROUPS ON THE DIOXOLANE RINGS

Compounds							
R= $<^{CH_3}_{CH_3}$	**21**	**18**	**22**	**19**	**23**	**20**	**24**
	8.69	8.77[a,9]	8.74[9]	8.70[a]	8.71[9]	8.66[a]	8.70[9]
R= $<^{CH_2}_{CH_2}$	**5**	**9**	**6**	**10**	**7**	**11**	**8**
	8.44	8.53[a]	8.48	8.55	8.68	8.55	8.60
Differences	0.25	0.24	0.26	0.15	0.03	0.11	0.10

a) $CDCl_3$ was used as a solvent. Other data were observed in CCl_4.

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[6] E. J. Corey and D. Seebach, *Angew. Chem.*, **77**, 1134, 1135 (1965).

[7] J. L. Piere and Arnaud, *Bull. Soc. Chim. Fr.*, **1967**, 1690.

[8] K. Tori and K. Kitahonoki, *J. Amer. Chem. Soc.*, **87**, 386 (1965) and the literature cited.

[9] T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, and S. Kagawa, This Bulletin, **45**, 1144 (1972).

Experimental

NMR spectra were taken on JEOL Co. Model 3H60 and Hitachi Model H60 spectrometers.

Ethyl 2,2-Ethano-3-ketobutyrate (**4**). An ethanolic solution prepared from 46 g of sodium and 900 ml of ethanol was added dropwise over a period of 6 hr with stirring, to a mixture of 130 mg of ethyl acetoacetate and 188 g of ethylene bromide. The temperature was maintained so that the the mixture was just refluxed. After addition was completed, the reaction mixture was further refluxed for 14 hr with stirring and concentrated under reduced pressure at temperatures below 50°C until most of the ethanol was removed. The residue was extracted with benzene several times and the combined extracts were washed with a saturated salt solution and dried. After evaporation of the solvent, the crude product was distilled to yield 39.1 g of an oil boiling at 85—90°C/25 mmHg. The distillate was dissolved in benzene and washed with 10% aqueous potassium hydroxide solution several times and then with a saturated salt solution and dried. Evaporation of the solvent gave 37.4 g (24%) of desired cyclopropane derivative: IR (neat) 3050, 1725, 1685 cm^{-1}.

Ethyl 2,2-Ethano-3,3-ethylenedioxybutyrate (**5**). A mixture of 115 g of **4**, 134 g of ethylene glycol, 300 mg of *p*-toluenesulfonic acid and 370 m*l* of benzene was refluxed for 46 hr. The water formed was removed by azeotropic distillation with a Dean-Stark separator. After cooling down to room temperature the reaction mixture was washed with a saturated sodium bicarbonate solution and then with water and dried. Evaporation of the solvent gave crude product which, on distillation, gave 100 g (68%) of the desired ketal; bp 127—137°C/20 mmHg; IR (neat) 1725 cm^{-1}; NMR τ(CCl_4) 9.00 (4H, m, cyclopropane), 8.73 (3H, t, J=7 Hz, $\underline{CH_3}CH_2O$), 8.44 (3H, s, CH_3CO), 6.16 (4H, s, OCH_2CH_2O), 5.96 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$).

Found: C, 59.98; H, 8.06%. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05%.

1-Methanesulfinyl-3,3-ethano-4-ethylenedioxy-2-pentanone (**9**). A portion of ether (210 m*l*) and 42.2 g of ester **5** were added dropwise over a period of 1 hr to a dimethyl sulfoxide solution of methanesulfinyl 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 and stirring was continued for additional 1.5 hr at room temperature and the reaction mixture was then poured into about 1 *l* of water washed three times with benzene, neutralized with diluted acetic acid to a pH of 5—6 (pH paper), and extracted five times with chloroform. The combined extracts were washed with a saturated salt solution until the washings were no longer acidic, dried over sodium sulfate and evaporated to yield 44.5 g (91%) of keto sulfoxide **10** as a pale yellow crystalline solid. A sample was recrystallized from ethyl acetate for analysis: mp 41—43°C; IR (Nujol) 1680, 1045 cm^{-1}; NMR τ($CDCl_3$) 8.87 (4H, bs, cyclopropane), 8.53 (3H, s, CH_3), 7.32 (3H, s, CH_3SO), 6.07 (4H, s, OCH_2CH_2O), 5.99 and 5.73 (2H, ABq, J=15 Hz, CH_2SO).

Found: C, 51,65; H, 6.86%. Calcd for $C_{10}H_{16}O_4S$: C, 51.70; H, 6.94%.

1-Methanesulfenyl-1-acetoxy-3,3-ethano-4,4-ethylenedioxy-2-pentanone (**12**). A solution of 4.0 g of sulfoxide **9** in 40 g of acetic anhydride was gently refluxed for 3 hr. Most of the acetic anhydride was evaporated under reduced pressure and the residue was dissolved in chloroform, washed with a saturated sodium bicarbonate solution and a saturated salt solution and dried. Removal of the solvent gave an oil which was chromatographed on silica gel to give 3.8 g (79%) of crystalline product; mp 44—46°C; IR (Nujol) 1740, 1690, 1240, 1040 cm^{-1}; NMR τ(CCl_4) 8.7—9.4 (4H, m, cyclopropane), 8.45, (3H, s, CH_3), 8.12 (3H, s, CH_3S), 7.92 (3H, s, AcO), 5.9—6.3 (4H, m, OCH_2CH_2O), 3.62 (1H, s, SCHO).

Found: C, 52.74; H, 6.79%. Calcd for $C_{12}H_{18}O_5S$: C, 52.55; H, 6.62%.

1-Acetoxy-3,3-ethano-4,4-ethylenedioxy-2-pentanone (**13**). Aluminum amalgam freshly prepared from 2.4 g of aluminum foil was added with stirring to a solution of 2 g of the Pummerer reaction product in 120 m*l* of 10% aqueous ethanol. The mixture was stirred for 2 hr at room temperature, then filtered and the residue was washed with ethanol. The combined filtrate was concentrated under reduced pressure at a temperature below 50°C till the most of ethanol was removed. The residue was dissolved in ether and the solution was washed with water and dried over anhydrous sodium sulfate. Evaporation of the ether gave 1.2 g of the crude products which was subjected to preparative vpc (column: Apiezon Grease (1 m), at 175°C, carrier gas: He 120 m*l*/min) to give *ca.* 300 mg (25%) of methyl ketone **14** and 460 mg (30%) of the desired product: bp 89—92°C/1 mmHg; IR (neat) 1750, 1710, 1230, 1045 cm^{-1}; NMR τ(CCl_4) 8.9—9.2 (4H, m, cyclopropane), 8.51 (3H, s, CH_3), 7.90 (3H, s, AcO), 6.60 (4H, s, OCH_2CH_2O), 5.12 (2H, s, CH_2-OAc).

Found: C, 57.89; H, 7.12%. Calcd for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07%.

3,3-Ethano-4,4-ethylenedioxy-2-pentanone (**14**.) Amalgamated aluminum freshly prepared from 2.7 g of aluminum foil was added with stirring to a solution of 2.32 g of the sulfoxide **9** in 150 m*l* of 10% aqueous tetrahydrofuran. The mixture was stirred for 1 hr in an ice-water bath, then filtered and the filtered solid was washed with tetrahydrofuran. The filtrate was concentrated till most of the tetrahydrofuran was removed. The residue was dissolved in ether, washed with water and dried over anhydrous sodium sulfate. Removal of the solvent gave 1.28 g of desired ketone: bp 45—46°C/1 mmHg; IR (neat) 1688, 1045 cm^{-1}; NMR τ(CCl_4) 8.91 (4H, s, cyclopropane), 8.44 (3H, s, CH_3), 7.79 (3H, s, CH_3CO), 6.08 (4H, s, OCH_2CH_2O).

1-Methanesulfinyl-1-acetoxy-3,3-ethano-4,4-ethylenedioxy-2-pentanone (**15**). Hydrogen peroxide (30% solution, 500 mg, 2 equivalent) was added to a solution of 450 mg of the Pummerer reaction product **12** in 5 m*l* of acetic acid. The solution was kept at a temperature below 10°C for 20 hr, neutralized with saturated sodium carbonate solution and extracted with benzene several times. The combined extracts were dried over anhydrous magnesium sulfate and the solvent was removed to give an oil. The oil was purified by silica gel chromatography to yield 122 mg (26%) of the sulfoxide; IR (neat) 1745, 1690 cm^{-1}; NMR τ($CDCl_3$) 9.5—8.0 (4H, m, cyclopropane), 8.36 (3H, s, CH_3), 7.7 (3H, s, AcO), 7.46 (3H, s, CH_3SO), 6.3—5.7 (4H, m, OCH_2CH_2O), 3.05 $\left(1H, s, OSHC\langle{}^{OAc}_{CO}\right)$.

1,1-Trimethylenedithio-3,3-ethano-4,4-ethylenedioxy-2-pentanone (**6**). A solution of 7 g of *n*-butyl bromide in 10 m*l* of ether was added dropwise to 0.8 g of lithium metal covered with 20 m*l* of ether at -30—-40°C and stirred for 1.5 hr at 0—10°C. To the resulting solution was added dropwise 4.3 g of 1,3-dithiane in 70 m*l* of tetrahydrofuran at -30—-40°C and stirred. To the solution thus prepared was added dropwise 7 g of ester **5** in 10 m*l* of tetrahydrofuran at −60—−70°C with stirring. The reaction mixture was allowed to stand at the same temperature range for 3 days and then poured into water. The solution was acidified with dilute hydrochloric acid and extracted with *n*-hexane. The extract was washed with a saturated salt solution and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was distilled to give 4.2 g (45%) of **6**: bp 146°C/2 mmHg which was soon crystallized, mp 59—60°C; IR (nujol) 3030, 1675, 1040 cm^{-1}; NMR τ(CDCl$_3$) 8.90 (4H, bs, cyclopropane), 8.49 (3H, s, CH$_3$), 6.3—8.3 (6H, m, S(CH$_2$)$_3$S), 6.09 (4H, s, OCH$_2$CH$_2$O), 5.18 $\left(\mathrm{1H,\ s,\ COCH}\langle^{\mathrm{S}}_{\mathrm{S}}\right)$.

Found: C, 52.43; H, 6.86%. Calcd for $C_{12}H_{18}O_3S_2$: C, 52.52; H, 6.61%.

*1,1-Trimethylenedithio-3,3-ethano-4,4-ethylenedioxy-2-pentanol (**7**).* To a solution of ketone **6**$^{9)}$ in dry ether was added a solution of excess lithium aluminum hydride in dry ether and stirred overnight at room temperature. The mixture was cooled in an ice bath and excess reagent was decomposed with a small amount of water. The mixture was extracted several times with ether. The extract was dried and concentrated to give a paste: IR (neat) 3400, 1040 cm^{-1}; NMR τ(CCl$_4$) 9.40 (4H, s, cyclopropane), 8.57 (3H, s, CH$_3$), 6.38 (1H, d, *J*=7 Hz, C$\underline{\mathrm{H}}$OH), 6.19 4H, s, OCH$_2$CH$_2$O), 5.66 (1H, d, *J*=7 Hz, SCHS); *m/e*: 276 (M$^+$).

*Acetate **8**.* A sample of alcohol **7** was acetylated with acetic anhydride and pyridine in the usual manner to give acetate **8** as a crystalline mass: mp 77—78°C; IR (Nujol) 1730, 1240, 1050 cm^{-1}; NMR τ(CCl$_4$) 8.4—9.7 (4H, m, cyclopropane), 8.55 (3H, s, CH$_3$), 7.90 (3H, s, AcO), 6.7—8.2 (6H, m, S(CH$_2$)$_2$S), 6.10 (4H, bs, OCH$_2$CH$_2$O), 5.77 (1H, d, *J*=10 Hz, SCHS), 5.09 (1H, d, *J*=10 Hz, AcOC$\underline{\mathrm{H}}$).

Found: C, 52.67; H, 7.01%. Calcd for $C_{14}H_{22}O_8$: C, 52.82; H, 6.97%.

*1-Methanesulfinyl-3,3-ethano-4,4-ethylenedioxy-2-pentanol (**10**).* To a solution of 1.97 g of **9** in 10 m*l* of ethanol was added a solution of 80 mg of sodium borohydride in 2 m*l* of ethanol. The mixture was allowed to stand overnight at room temperature with stirring. After removal of most of the ethanol under reduced pressure, the residue was dissolved in water and extracted with chloroform. The aqueous phase was concentrated under reduced pressure and extracted with chloroform. The combined extracts were dried over sodium sulfate and the solvent was removed to give 1.7 g (84%) of colorless paste which crystallized gradually. A sample of the product was recrystallized from ethyl acetate: mp 120—122°C; IR (Nujol) 3200, 1045, 1025, 995 cm^{-1}; NMR τ(CDCl$_3$) 9.1—9.5 (4H, m, cyclopropane), 8.55 (3H, s, CH$_3$), 8.03 (1H, s, OH), 7.33 (3H, s, CH$_3$SO), 7.07 (2H, d, *J*=6 Hz, SOCH$_2$), 6.06 (4H, s, OCH$_2$CH$_2$O), 5.77 (1H, t, *J*=6 Hz, OCH).

Found: C, 51.33; H, 7.67%. Calcd for $C_{10}H_{18}O_4S$: C, 51.27; H, 7.75%.

*Acetate **11**.* A sample of above alcohol **10** was acetylated with acetic anhydride and pyridine in the usual manner to give acetate **11**: IR (neat) 1745, 1240, 1045 cm^{-1}; NMR τ (CCl$_4$) 9.1—9.5 (4H, m, cyclopropane), 8.55 (3H, s, CH$_3$), 7.95 (3H, s, AcO), 7.45 (3H, s, CH$_3$SO), 6.88 (2H, d, *J*=6 Hz, CH$_2$SO), 6.10 (4H, s, OCH$_2$CH$_2$O), 4.98 (1H, t, *J*=6 Hz, C$\underline{\mathrm{H}}$OAc); *m/e*: 276 (M$^+$).

*1-Methanesulfinyl-3,3-dimethyl-4,4-ethylenedioxy-2-pentanol (**19**).* To a solution of 249 mg of 1-methanesulfinyl-3,3-dimethyl-4,4-ethylenedioxy-2-pentanone (**18**) in 10 m*l* of water was added a solution of 15 m*l* of sodium borohydride in 1 m*l* of water. The mixture was stirred in an ice bath for 3 hr and left in a refrigerator overnight. The mixture was extracted several times with chloroform and the extract was dried and evaporated to give 202 mg (81%) of a crystalline mass which was recrystallized from ethyl acetate: mp 140—144°C; IR (neat) 3200, 1030, 1005 cm^{-1}; NMR τ (CDCl$_3$) 9.05 (3H, s, CH$_3$), 8.98 (3H, s, CH$_3$), 8,70 (3H, s, CH$_3$), 7.26 (3H, s, CH$_3$SO), 6.8—7.5 (2H, m, CH$_2$SO), 6.06 (4H, s, OCH$_2$CH$_2$O), 5.80 (1H, d, *J*=8 Hz, OCH).

*Acetate **20**.* A sample of alcohol **19** was acetylated with acetic anhydride and pyridine in the usual manner to give acetate **20**: IR (neat) 1740, 1235, 1035 cm^{-1}; NMR τ (CDCl$_3$) 9.00 (6H, s, 2×CH$_3$), 8.66 (3H, s, CH$_3$), 7.90 (3H, s, AcO), 7.39 (3H, s, CH$_3$SO), 6.3—7.3 (2H, m, CH$_2$SO), 6.06 (4H, s, OCH$_2$CH$_2$O), 4.40 (1H, d, *J*=10 Hz, of *d*, *J*=2.5 Hz, OCH).