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SYNTHESIS OF ILLUDIN S

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In a previous paper, the total synthesis of dl-illudin M (10) was reported. In this paper we wish to describe synthesis of dl-illudin S diacetate (13)[2,3,4] through a similar sequence of reactions. Since reconversion of optically active illudin S diacetate to illudin S by treatment with aqueous sodium carbonate has been performed, the present study represents formally total synthesis of illudin S.

A mixture of *cis* and *trans* forms (1 : 3) of the cyclopentenone 2[5,6,7] was obtained in high yield from 2-methyl-2-carbethoxycyclopentanone[8] and each stereoisomer was separated by preparative VPC[9]. The Michael condensation of β-ketosulfoxide 1[1] with the *trans* compound 2 (2 equiv KOBu^t-Bu^{t}OH, rt, 2 hr) afforded in 70% yield a single adduct 3[7], mp 139-140°; ir (nujol) 1745, 1675, 1230 cm^{-1}; nmr τ(CCl$_4$) 9.08 (3H, s, C-CH$_3$), 8.46 (3H, s, O-C-CH$_3$), 8.00 and 7.92 (each 3H, s, 2X AcO), 7.42 (3H, s, SO-CH$_3$), 5.42 (1H, d, J = 7Hz, OS-CH), 4.46 (1H, d, J = 9Hz, AcOCH). The J value of 9Hz due to the proton attached to carbon bearing acetoxy group suggested[10,11] that the newly formed C$_4$-C$_{1'}$ bond in 3 was *trans* to the C$_3$ acetoxy group.

Treatment of 3 with methoxyacetic anhydride and pyridine afforded quantitatively an oily Pummerer rearrangement product 4[12], ir (neat) 1740, 1685, 1230 cm^{-1}; nmr τ(CCl$_4$) 9.08 (3H, s, C-CH$_3$), 8.58 (3H, s, O-C-CH$_3$), 8.05 (3H, s, S-CH$_3$), 8.00 (6H, s, 2xAcO), 6.55 (3H, s, -OCH$_3$), 6.04 (6H, bs,

$O-CH_2-CH_2-O$ and $COCH_2O$), 4.24 (1H, d, J = 9Hz, AcO-CH), which, on being set aside for 3 days in ethanol at room temperature, was converted to a methyl ketone 5, ir (neat) 3500, 1750, 1690, 1235 cm^{-1}; nmr $\tau(CCl_4)$ 9.08 (3H, s, $C-CH_3$), 8.0 (3H, s, SCH_3), 7.94 and 7.90 (each 3H, s, 2xAcO), 7.80 (3H, s, $COCH_3$), 4.30 (1H, d, J = 9Hz, AcOCH). Treatment of the ketone 5 with potassium t-butoxide at room temperature afforded 7, ir (neat) 1750, 1710, 1625, 1240 cm^{-1}; nmr $\tau(CCl_4)$ 9.02 (3H, s, $C-CH_3$), 8.04 and 7.96 (each 6H, s, 3xAcO and $S-CH_3$), 8.00 (3H, d, J = 1Hz, $=\!\diagup CH_3$) 4.10 (1H, d, J = 9Hz, AcOCH). Grignard reaction of 7 with methylmagnesium iodide gave a semithioketal 8[13], ir (neat) 3480, 1745, 1710, 1620, 1235 cm^{-1}; nmr $\tau(CCl_4)$ 9.01 (3H, s, $C-CH_3$), 8.72 (3H, s, $HO-C-CH_3$), 8.02, 7.92 and 7.90 (15H, 3xs, 3xAcO, SCH_3 and $=\!\diagup CH_3$), 4.30 (1H, d, J = 9Hz, AcOCH). The semithioketal 8 was then reduced by sodium borohydride in THF to a diol 9, ir (neat) 3500, 1740, 1245 cm^{-1}; nmr $\tau(CCl_4)$ 9.10 (3H, s, $C-CH_3$), 8.76 (3H, s, $HO-C-CH_3$), 8.68 (3H, d, J = 2.5Hz, $=\!\diagup CH_3$) which was converted to illudin S monoacetate (12) by treatment with mercuric chloride in aqueous acetone. The ir spectrum and Rf value on tlc of the product were completely identical with those of optically active form obtained by partial acetylation of natural illudin S. On acetylation the dl-monoacetate gave the dl-diacetate 13 completely identical spectroscopically (ir in CCl_4) and chromatographically (tlc with various solvent systems) with optically active form.

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5 This compound was prepared from 2-methyl-2-carbethoxycyclopentanone by the sequence: 1) ketalization with ethylene glycol, 2) reduction with lithium aluminum hydride, 3) acetylation, 4) deketalization, 5) bromination and dehydrobromination, 6) bromination with NBS and 7) reaction with silber acetate.

6 Stereochemical studies of *cis* and *trans* forms of **2** will be described elsewhere.

7 Satisfactory elemental analysis has been obtained for this compound.

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9 The column used was 3m, 30% DGSP column at 170° and He flow rate: 100 ml/min.

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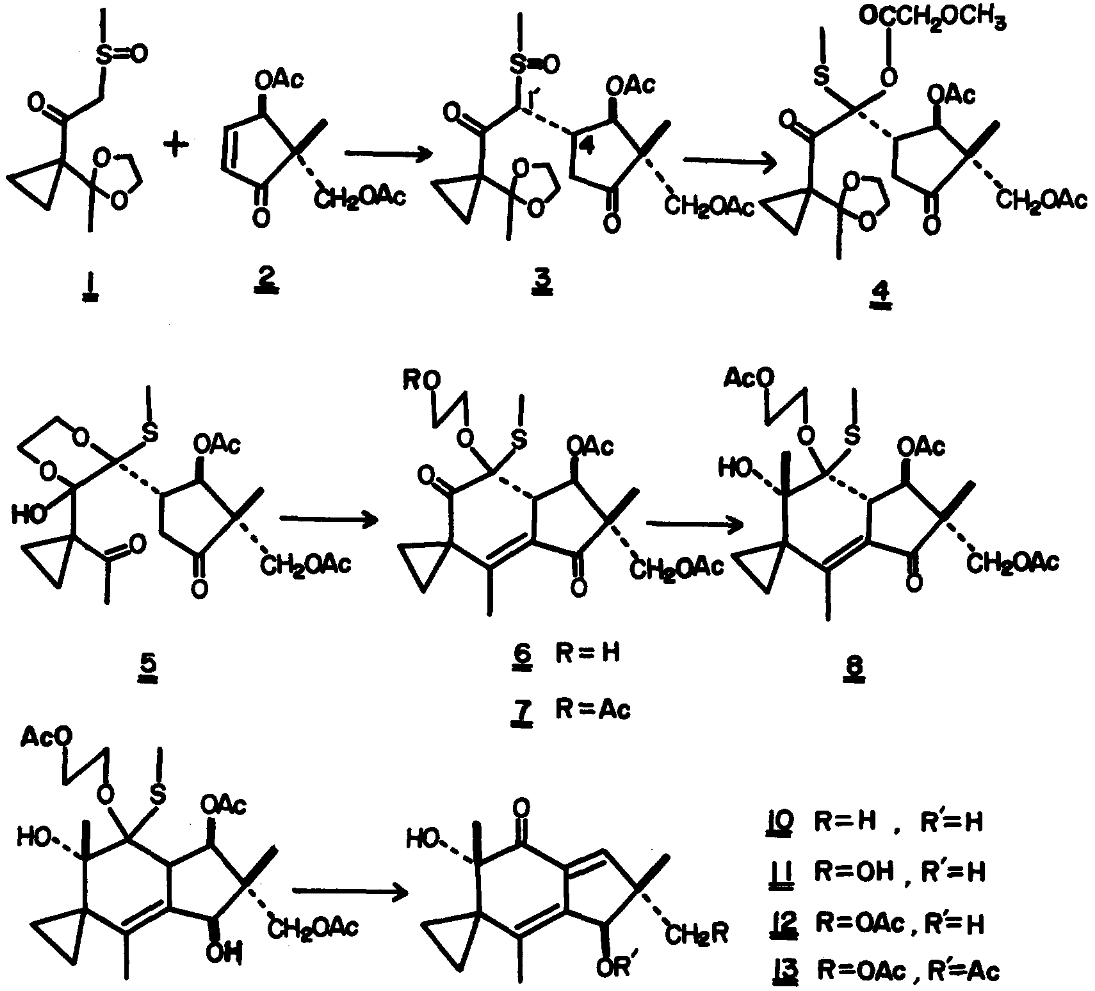
12 In contrast to the case of the synthesis of illudin M, acetic anhydride reacted extremely slowly, requiring 10 days at room temperature and the Pummerer product thus formed could not be caused to change to methyl ketone **5**.

13 In a previous paper[10], we reported that compound **i** underwent addition of of methylmagnesium iodide to give selectively **ii**. However detailed study of the product showed a very small amount of **iii** had been produced. The methyl group at C_5 of **ii** exhibited a signal at 8.77 while the corresponding peak of **iii** appeared at 9.07. The low field chemical shift (8.77) of the methyl group of **8** shows clearly the configuration at C_5 as shown in the formula.

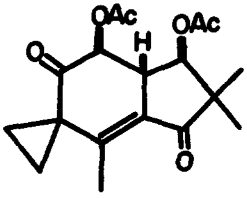


1 2 3 4

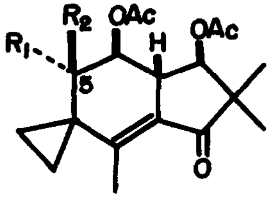
5 6 R=H 7 R=Ac 8

9

10 R=H , R'=H
11 R=OH , R'=H
12 R=OAc , R'=H
13 R=OAc , R'=Ac



i



ii R_1=OH , R_2=CH_3
iii R_1=CH_3, R_2=OH