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SYNTHESIS OF ILLUDINS II.[1] FUNCTIONALIZED ILLUDANE

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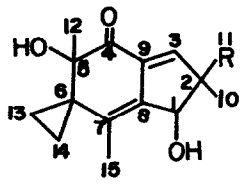
In an earlier paper[2] a stereospecific synthesis of the compound III, which has the unique non-isoprenoid skeleton and some structural features of illudins (I and II)[3),4)], was described. In this paper we wish to report a stereospecific synthesis of a further functionalized compound IV, which is expected to be a suitable intermediate in the total synthesis of illudin M. The route is outlined in Fig. 1.

The starting material 4-acetoxy-5,5-dimethylcyclopent-2-en-1-one (VI) was prepared from 5,5-dimethylcyclopent-2-en-1-one[2]. The cyclopentenone was at first brominated by N. B. S. to give 4-bromo-5,5-dimethylcyclopent-2-en-1-one ν_{max}^{neat} 1720, 1585, 835 cm^{-1}; τ^{CCl_4} 8.80(3H)s.*), 8.76(3H)s., 5.02(1H)q.(J=3c/s, 1.5c/s), 3.78(1H)d.(J=6c/s) of d.(J=1.5c/s), 2.42(1H)q.(J=6c/s, 3c/s) (59%), which in turn was converted by treating with silver acetate in acetic acid into VI, b.p. 94-95°/20mm, $C_9H_{12}O_3$†) ν_{max}^{neat} 3050, 1740, 1725, 1600, 1235

*) Multiplicities are indicated by the usual symbols s. singlet, d. doublet, t. triplet, q. quartet, m. multiplet, AB AB type quartet and b. broad.

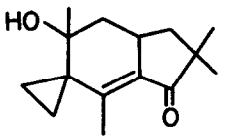
†) Satisfactory analytical data were obtained for all the new compounds indicated by molecular formulae.

Fig. 1

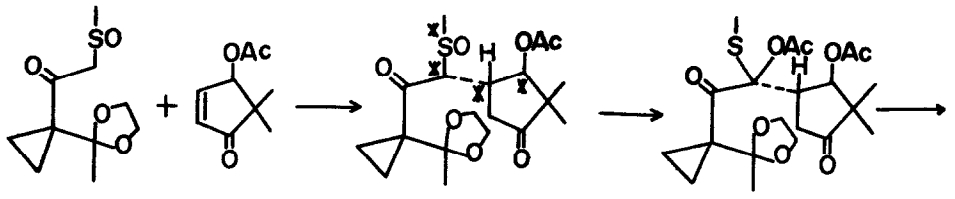


Illudin S[3)4)] (I) R=CH_2OH

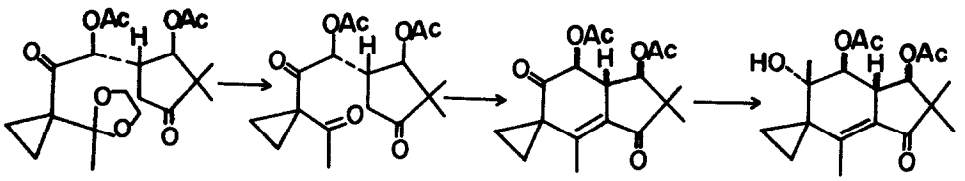
Illudin M[4)] (II) R=CH_3



III



V VI VII VIII



IX X XI IV

cm^{-1}; τ^{CCl_4} 9.05(3H)s., 8.83(3H)s., 7.93(3H)s., 4.52(1H)q.(J=3c/s, 1c/s), 3.78(1H)q.(J=6c/s, 1c/s), 2.65(1H)d.(J=6c/s) of d.(J=3c/s) (72%). The Michael reaction of VI with V[2)] proceeded remarkably selectively and afforded a single adduct VII, m.p. 170-172°, $C_{19}H_{28}O_7S$ ν_{max}^{nujol} 1740, 1670, 1245, 1045 cm^{-1}; τ^{CDCl_3} 9.02(3H)s., 8.86(3H)s., 8.45(3H)s., 8.3-9.1(4H)m., 7.9(3H)s., 7.26(3H)s., 6.8-8.3(3H)m., 6.04(4H)s., 5.27(1H)d.(J=7c/s), 4.82(1H)d.(J=9c/s) in 58% yield, in spite of the presence of four asymmetric centers in VII.

Treatment of VII with acetic anhydride and pyridine at room temperature for a week converted VII to VIII, m.p. 119.5-120°, $C_{21}H_{30}O_8S$ ν_{max}^{nujol} 1745, 1690,

1220, 1045 cm^{-1}; τ^{CCl_4} 9.04(3H)s., 8.82(3H)s., 8.53(3H)s., 7.98(3H)s., 7.90(6H)s., 7.0-9.2(7H)m., 6.01(4H)b.s., 4.52(1H)d.(J=9c/s) (54%). Examination of the n.m.r. spectrum of the product VIII showed that the Pummerer reaction gave rise to a single product, although formation of an epimeric pair at C_4 is possible. Reduction of VIII with amalgamated aluminum in 90% ethanol gave an α-acetoxyketone IX (ν_{max}^{neat} 1745, 1710, 1230, 1045 cm^{-1}; τ^{CCl_4} 9.10(3H)s., 8.87 (3H)s., 8.4-9.5(5H)m., 8.38(3H)s., 8.10(3H)s., 7.85(3H)s., 7.0-8.0(2H)m., 5.6-6.3(4H)m., 4.68(1H)d.(J=9c/s), 4.29(1H)d.(1.5c/s)) (90%). This sequence of reactions, condensation of ester with methylsulfinyl carbanion, the Pummerer rearrangement and subsequent reductive fission of C-S bond may serve as a new, general route to α-acetoxyketones. The ketal group of IX was removed by boiling in acetone in the presence of a small amount of p-toluenesulfonic acid. The triketone X thus obtained was next converted by potassium tert-butoxide in tert-butanol to a cisoid enone XI, m.p. 159-160°, $C_{18}H_{22}O_6$ (ν_{max}^{nujol} 1755, 1730, 1700, 1610, 1250, 1230 cm^{-1}; τ^{CDCl_3} 8.92(3H)s., 8.85(3H)s., 8.0-8.9(4H)m., 7.95 (3H)d.(J=3c/s), 7.85(6H)s., 6.5-7.0(1H)m., 4.78(1H)d.(J=9c/s), 4.60(1H)d.(J=12 c/s) (70%).

Examination of the n.m.r. spectra of the compound XI and VII enabled us to deduce the stereochemistry of these two compounds. In the compound XI, the α,β-unsaturated carbonyl system, C_1, C_8 and C_7 must be at least nearly on a plane. Therefore the J_{AX} value of 9c/s indicates that H_A and H_X (Fig. 2) are both quasi-axial*) and the cyclopentanone ring adopts an envelope form as shown in IXa. Therefore H_A and H_X are trans. Next, since J_{BX} is 12c/s, H_B and H_X are both axial to the cyclohexenone ring, and hence are also trans to each other. In the compound VII, $J_{A'X'}$ is 9c/s, just as in the case of XI. Therefore the stereochemistry of VII is concluded to be expressed by VIIa.

Attack of methylmagnesium iodide to the C_5 carbonyl group of XI occurred

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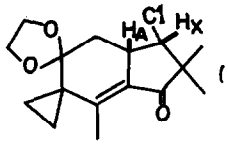
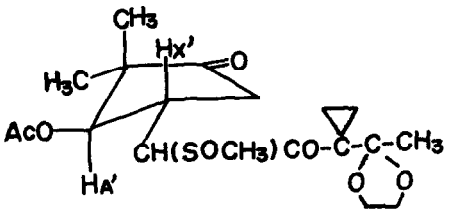
*) The J_{AX} values of all the related compounds obtained in this work were ca. 9c/s, while the compound (i) with axial chlorine exhibited a J_{AX} value of 4.5c/s.

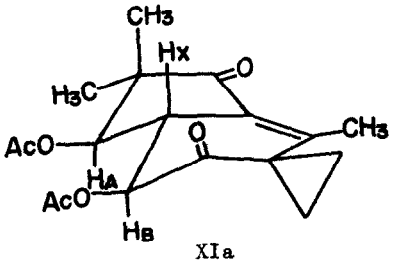


(i)

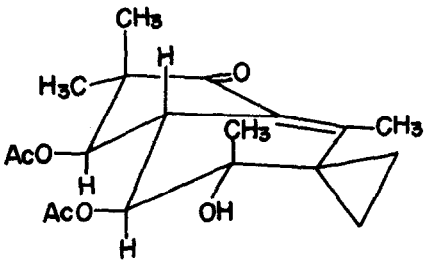
Fig. 2



VIa

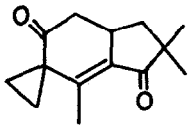


XIa

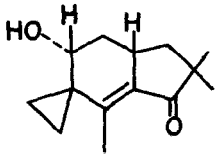


IVa

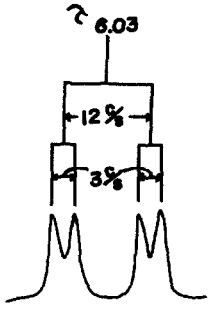
Fig. 3



XV



XIV



Low field part of
the n.m.r. spectrum of XIV

again stereoselectively to give a single crystalline product IV, m.p. 173-175°, $C_{19}H_{26}O_6$ ν_{max}^{nujol} 3440, 1750, 1715, 1705, 1605, 1265, 1235 cm^{-1}; τ^{CDCl_3} 8.91(3H) s., 8.82(3H)s., 8.77(3H)s., 8.05(3H)d.(J=2.5c/s), 7.85(6H)s., 4.95(1H)d.(J=9c/s), 4.92(1H)d.(J=11c/s). The model XIa shows that the upper site is less hindered to the attack. Then the stereochemistry of the compound IV is reasoned to be shown by IVa. Moreover, the n.m.r. spectrum of the compound XIV (Fig. 3), which was obtained by reduction of XV[2] with sodium borohydride indicates that the hydrogen atom at C_5 position is axial ($J_{AX} + J_{BX} = 12 + 3$ c/s) and attack of the reagent had occurred in fact from the upper site. The conformation of IV can thus be depicted as IVa.

The path leading to illudin M (II) is now under investigation.

REFERENCES

1) Presented at the 11th symposium on the chemistry of natural products (Japan), Kyoto, Oct. 1967, Abstracts, p. 120.

2) T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, N. Ito, T. Hisamitsu, T. Kamada and F. Sakan, Tetrahedron Letters No. 42 (1967).

3) T. Matsumoto, H. Shirahama, A. Ichihara, Y. Fukuoka, Y. Takahashi, Y. Mori and M. Watanabe, Tetrahedron 21, 2671 (1965); T. Matsumoto, Y. Fukuoka, A. Ichihara, Y. Mori, H. Shirahama, Y. Takahashi and M. Watanabe, Bull. Chem. Soc. Japan 37, 1716 (1964); K. Nakanishi, M. Ohashi, M. Tada and Y. Yamada, Tetrahedron 21, 1231 (1965).

4) T. C. McMorris and M. Anchel, J. Am. Chem. Soc. 87, 1594 (1965).