Tetrahedron Letters No.44, pp. 3913-3916, 1969. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF ILLUDOL (1) PROTOILLUDANE SKELETON

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(Received in Japan 5 July 1969; received in UK for publication 20 August 1969)

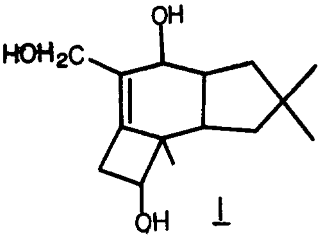
A structure 1 is assigned to a sesquiterpene illudol, isolated from Clitocybe illudens by Anchel et al.[1] We report herein a partially stereospecific synthesis of a protoilludane[2] skeleton 14. Although the stereochemistry of illudol is not yet clear, the compound 14 could be a valuable intermediate in the total synthesis of illudol. The route is shown in Scheme 1.

Reaction of 2[3] with bromomethyl ethyl ketone and sodium hydride in DMF-benzene (2:1) at 50° for 1 hr followed by refluxing the product in 20% aqueous perchloric acid overnight afforded 3, ν_{max} 1746, 1718 cm^{-1}; τ^{CCl_4} 8.96 (3H, t, J=7), 8.90 (3H, s), 8.82 (3H, s), 7.93 (2H, s), 7.63 (2H, q, J=7). The diketone 3 was treated with excess sodium hydride in refluxing benzene for 1.5 hr to give 4 ν_{max} 1715, 1670 cm^{-1}; τ^{CCl_4} 8.89 (3H, s), 8.81 (3H, s), 8.40 (3H, b.s.), 7.70 (2H, b.s.), which was reduced by catalytic hydrogenation to a single monoketone 5, ν_{max} 1748 cm^{-1}; τ^{CDCl_3} 9.05 (3H, d. J=7), 8.99 (3H, s), 8.29 (3H, s), (41% overall yield from 2). The monoketone 5 was next transformed to a benzylidene derivative, which was treated with ethanolic sodium borohydride under reflux for 2 hr and then acetylated with acetic anhydride-pyridine. The acetate was oxidized with ozone in ethyl acetate at -77° for 2 hr to give, after alkaline hydrolysis, a ketol 6, ν_{max} 3640, 1747 cm^{-1}.

Oxidation of 6 with bismuth trioxide in refluxing acetic acid for 2 hr afforded a single diosphenol ν_{max} 3320, 1710, 1650 cm^{-1}; τ^{CDCl_3} 9.01 (3H, s), 8.99 (3H, s), which was converted by treatment with acetic anhydride-pyridine overnight to an α-diketone enol acetate 7 (30% overall yield from 5). The n.m.r. spectrum of

7 shows a signal at τ^{CDCl_3} 8.80 (3H, s) due to vinylic methyl, which indicates that the enolization occurred to one direction shown in formula 7, in addition to the expected methyl signals at τ^{CDCl_3} 8.98 (6H, s) and 7.74 (3H, s). The absorption bands at 1785, 1720, 1660 and 1200 cm^{-1} in the i.r. spectrum of 7 also indicate the presence of α-diketone enol acetate.

In the hope of construct the four membered ring in the protoilludane skeleton, a mixture of 7 and 1,1-diethoxyethylene was then irradiated with high-pressure mercury lamp (75 W) under cooling with water for 6 hr to afford a single cis-anti-cis tricyclic compound 8, ν_{max} 1760, 1745, 1235, 1220, 1070, 1049 cm^{-1}; τ^{CDCl_3} 9.01 (3H, s), 8.91 (6H, s), 8.80 (3H, t, J=7), 8.74 (3H, t, J=7), 7.92 (3H, s), 6.70-6.40 (4H, m) in 50% yield. Approach of diethoxyethylene from the upper side of the convex is assumed to be sterically favorable. This assumption is supported by the small difference of chemical shifts (at most 0.1 ppm) of gem methyl groups in 8. In the syn compound these two methyl groups would exhibit their respective signals at quite different positions, since one of the methyl groups is very close to an ethereal oxygen atom. The orientational mode of this type of photocycloaddition of diethoxyethylene to α-acetoxyenone system has been shown by spectroscopic data of this and derived compounds and supported by



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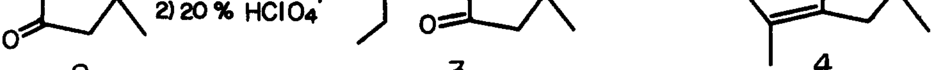
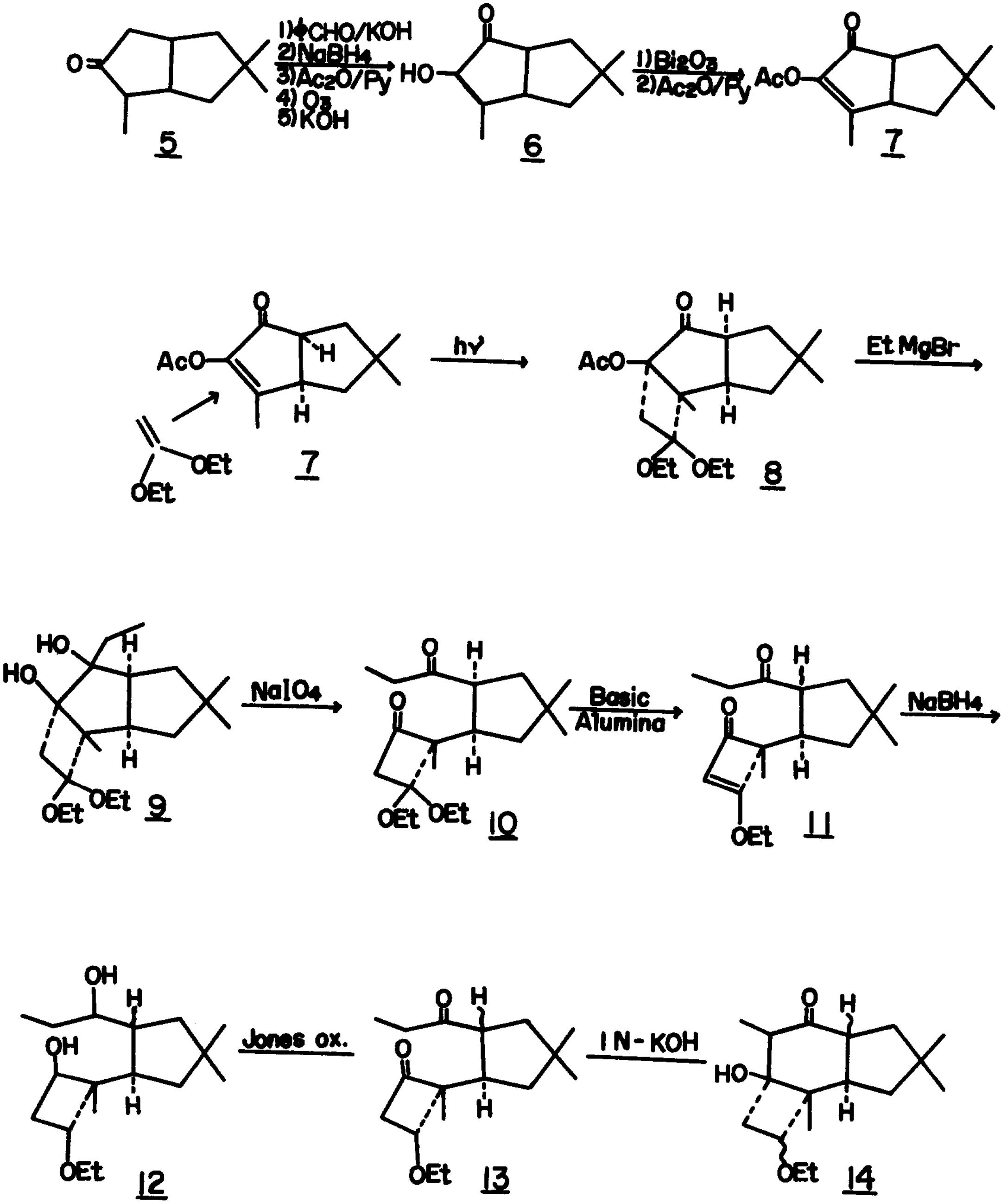


2 3 4


1) ϕCHO/KOH
2) NaBH4
3) Ac2O/Py
4) O3
5) KOH
1) Bi2O3
2) Ac2O/Py
hν
Et MgBr
NaIO4
Basic Alumina
NaBH4
Jones ox.
1 N-KOH
5
6
7
7
8
9
10
11
12
13
14

Scheme 1

chemical evidence in the case of other simpler bicyclic product.[4] The Grignard reaction of 8 and excess ethylmagnesium bromide in ether at room temperature for 1 hr afforded a diol 9 in 52% yield. The n.m.r. spectrum of 9 contains peaks at τ^{CDCl_3} 9.01 (3H, s), 8.95 (3H, s), 8.89 (3H, s), 7.91 (2H, s, CH_2 of cyclobutane) and 6.90-6.10 (4H, symmetrical 8 lines). The i.r. spectrum shows an absorption band due to hydroxyl groups at 3480 cm^{-1} and absence of two carbonyl groups.

Oxidative cleavage of 9 with excess sodium periodate in ethanol-water-pyridine (1:1:0.08) at room temperature overnight proceeded smoothly to give a diketone 10, νmax 1783, 1710 cm^{-1}; τ^{CDCl_3} 8.97 (3H, s), 8.88 (3H, s), 8.80 (3H, t, J=7), 8.82 (3H, t, J=7), 6.94 (2H, s, CH_2 of cyclobutane), 6.53 (2H, t, J=7), 6.52 (2H, t, J=7) in 52% yield. Adsorption of 10 on a basic alumina column overnight afforded 11 in 51% yield. The n.m.r. spectrum includes the following signals; τ^{CDCl_3} 9.02 (3H, s), 8.98 (3H, s), 8.82 (3H, s), 8.52 (3H, t, J=7), 5.95 (2H, q, J=7) and 5.30 (1H, s). The signal at 5.30 should be ascribed to an α-olefinic proton of the cyclobutenone 11 and confirms that the orientation of photocycloaddition is as in 8. The i.r. spectrum shows bands of cyclobutenone at 1760 and 1580 cm^{-1}. The cyclobutenone 11 was treated with ethanolic sodium borohydride at room temperature for 3 hr and then oxidized by Jones reagent to give a diketone 13 (νmax 1780, 1715 cm^{-1}). The diketone 13 finally cyclized by treatment with ethanolic 1 N potassium hydroxide at room temperature for 1 hr to the protoilludane skeleton 14 νmax 3650, 1710 cm^{-1}; τ^{CDCl_3} 8.97 (3H, d, J=6), 8.93 (3H, s), 8.75 (6H, s), 6.65 (2H, q, J=6), which has most probably the stereochemical structure shown in the figure 14. Synthesis of illudol and its stereoisomers through this intermediate 14 are being continued.

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