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TOTAL SYNTHESIS OF *dl*-ILLUDOL

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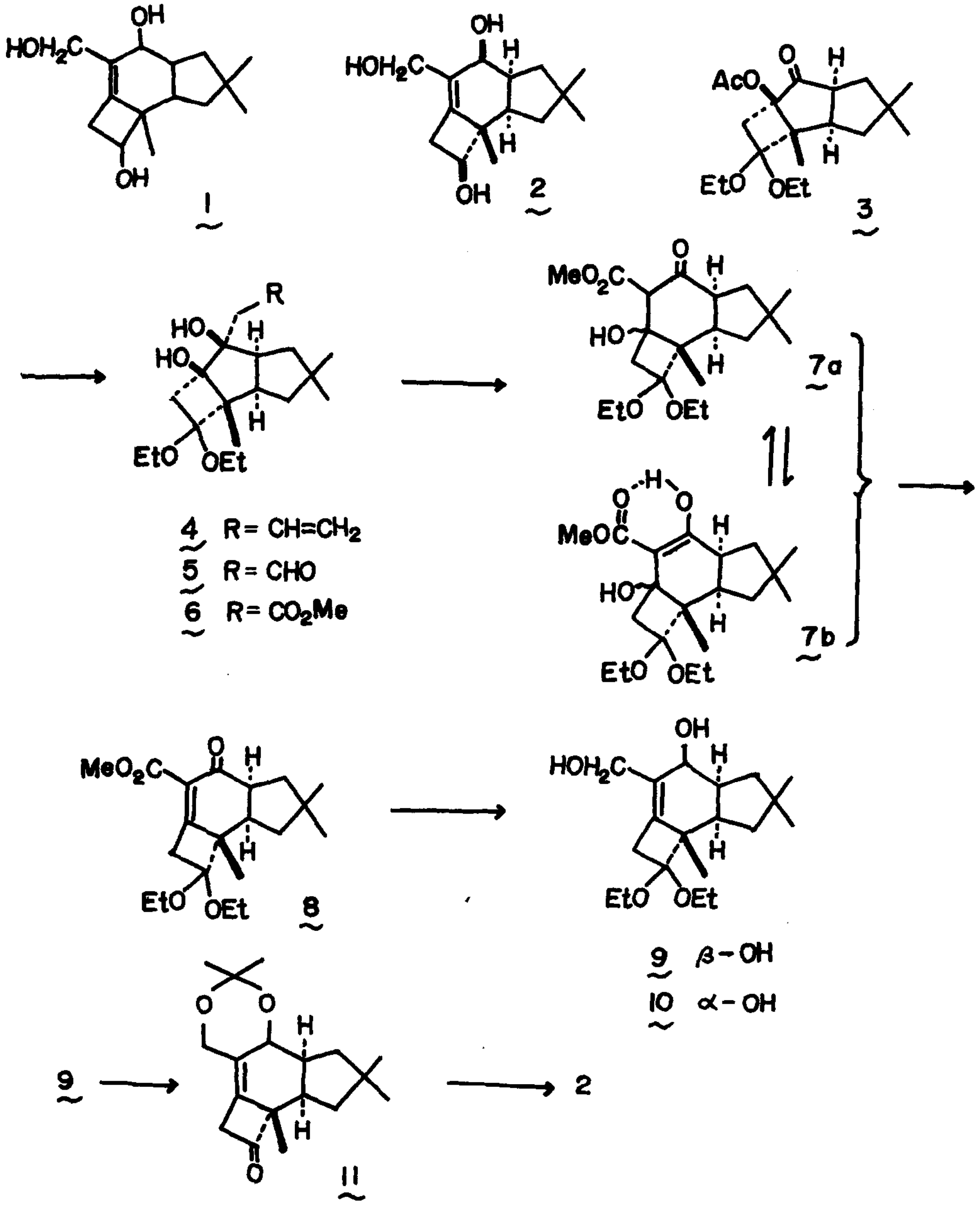
Illudol, a sesquiterpene alcohol isolated from *clitocybe illudens*, has been characterized as **1** by Anchel *et al.*[1]. Although the stereochemistry of the sesquiterpene has not yet been reported, the structural relationship with other illudoids suggests the stereochemistry **2** except for the configurations of the secondary hydroxyl groups.[2] We should like to report here a synthesis of the racemic compound **2**, which does exhibit spectra completely identical with those of natural illudol.

The *cis-anti-cis* cycloadduct **3** [3,4,5] was treated with allylmagnesium bromide in abs ether (25°, 1 hr) to yield a diol **4** [4] (65%, $\nu_{OH}^{0.03M\ CCl_4}$ 3534cm^{-1}; nmr δ 0.97 (6H)s, 1.08 (3H)s, 1.11 (6H)t, 2.00 (2H)s, (cyclobutane), 3.45 (4H)q)[6] which was ozonized in ethyl acetate (-78°, 1 hr reductive cleavage with potassium iodide) to give an aldehyde **5**.[3,4] Oxidation of the aldehyde function of **5** with silver oxide in dioxane-7% aq sodium hydroxide (2:1, 5°, 1 hr) followed by methylation with diazomethane afforded a dihydroxy ester **6** [3,4,6] mp 77-78° (50%). Oxidative cleavage of **6** with sodium periodate in methanol-water-pyridine (1:1:0.1, 25°, 20 hr)and concomitant aldol condensation led to an isomeric mixture of **7a** and **7b** [4] (1:1 by nmr, 98%, ir (neat) 1760, 1720, 1648 and 1610cm^{-1}; nmr δ 0.90 (3H)s, 1.01 (3H)s, 1.17 (6H)t, 1.23 (3H)s, -2.47 (0.5H)s), which on dehydration by methanesulfonyl chloride-pyridine (51°, 3 hr) afforded an enone **8** [7,8] mp 83-84° (52%, ir 1735, 1718 and 1680cm^{-1}; nmr δ 0.99 (3H)s, 1.11 (6H)s, 3.31 (2H)s, (-CH_2- on the four-membered ring)). Reduction of **8** with sodium dihydro-bis(2-methoxyethoxy)aluminate in benzene (25°, 20 hr) gave a 47% yield of a diol **9** [7,9] (ir 3350, 1720cm^{-1}; nmr 1.00 (3H)s, 1.15 (3H)s, 1.20 (3H)s, 2.80 (2H)s, 3.42 (2H)s) and a 17% yield of an epimer **10** [7],



1
2
3
4 R= CH=CH$_2$
5 R= CHO
6 R= CO$_2$Me
7a
7b
8
9 β-OH
10 α-OH
11
9
2
HOH$_2$C
OH
AcO
EtO
OEt
MeO$_2$C
MeOC
HO
H

mp 125-127° (ir 3400 and 1720cm^{-1}; nmr δ 1.00 (6H)s, 1.10 (3H)s, 2.75 (2H) bs, 3.60 (2H)bs). Treatment of **9** with acetone and p-toluenesulfonic acid led to an unstable acetonide **11** (68%, ir 1890 and 1728cm^{-1}; nmr δ 1.08, 1.17, 1.26, 1.38 (each 3H,s)). Reduction of **11** with sodium dihydro-bis(2-methoxyethoxy)aluminate in benzene (25°, 24 hr) afforded stereospecificially the desired *dl*-illudol (70%).[10] The spectral data (*m/e* 234.1578 [Calcd for $C_{15}H_{22}O_2$ (M^+-H_2O) 234.1619], 216.1608 [Calcd for $C_{15}H_{20}O_1$ (M^+-H_2Ox2) 216.1614]; ir 3350, 1113 and 1005 cm^{-1}; nmr (pyridine-d_5) δ 0.92 (3H)s, 1.04 (3H)s, 1.27 (3H)s, 4.21 (1H)t,J=7Hz, 4.70 (2H)s, 4.95 (1H)m, 6.01 (3H)s) and the R_f values on tlc of synthetic illudol were completely identical with those of natural illudol.

Acknowledgement

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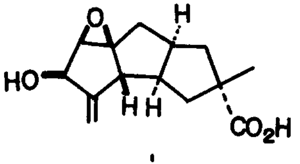
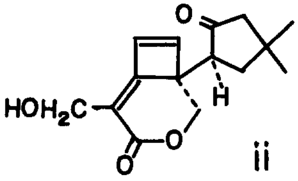
References

1. T. C. McMorris, M. S. R. Nair, and M. Anchel, *J. Am. Chem. Soc.*, **89**, 4562 (1967). For the synthesis of a biogenetically related compound, illudin M, see T. Matsumoto, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, S. Matsumoto, and S. Nishida, *ibid.*, **90**, 3280 (1968).
2. The absolute structures of hirsutic acid (F. W. Comer, F. McCapra, I. H. Qureshi, and A. I. Scott, *Tetrahedron* **23**, 4761 (1967)) and of fomannosin (J. A. Kepler, M. E. Wall, J.E. Mason, C. Basset, A. T. McPhail, and G. A. Sim, *J. Am. Chem. Soc.*, **89**, 1260 (1967)) have been shown as i and ii respectively. If the absolute configuration at the A/B ring juncture of illudol **1** is identical with that of i and the absolute configuration at the quarternary carbon atom on the four-membered ring is common in i and ii, illudol should have a *cis-anti* carbon framework of **2**.

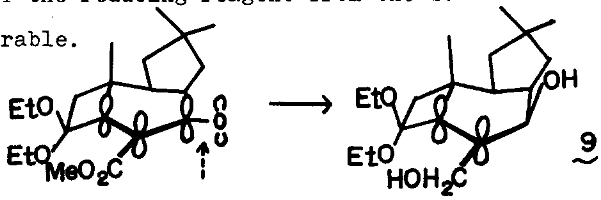


i



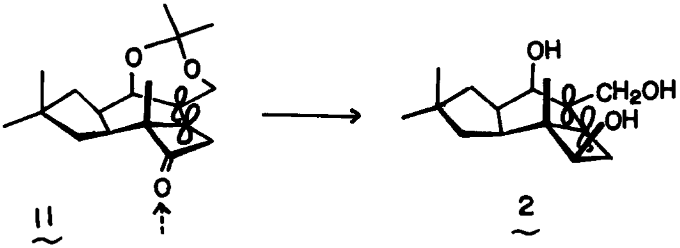
ii

3. Reasonable ir and nmr spectra have been obtained for this compound.
4. The molecular formula of this compound has been confirmed by elementary analysis and by mass spectrometry.
5. S. Kagawa, S. Matsumoto, S, Nishida, S. Yü, J. Morita, A. Ichihara, and T. Matsumoto, Tetrahedron Lett., No. 44, 3913 (1969).
6. All the nmr spectra were taken in deuterochloroform solution with TMS as internal standard.
7. The molecular formula of this compound has been ascertained by exact mass spectrometry.
8. Inspection of molecular models indicates that in this case the cis-perhydroindenone structure **8** is more stable than the trans isomer,because of the flattened conformation of the six-membered ring.
9. The hydroxyl/angular methyl cis structure is assigned for the major product **9**, since attack of the reducing reagent from the less hindered side of **8** is clearly more favorable.



8 **9**

10. The configuration of newly formed hydroxy group is cis relative to the angular methyl group by the similar reason as in the footnote 9.



11 **2**