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Total Synthesis of Liverwort Sesquiterpene Ketone (±)-Chiloscyphone *via* Intramolecular Aldol Condensation

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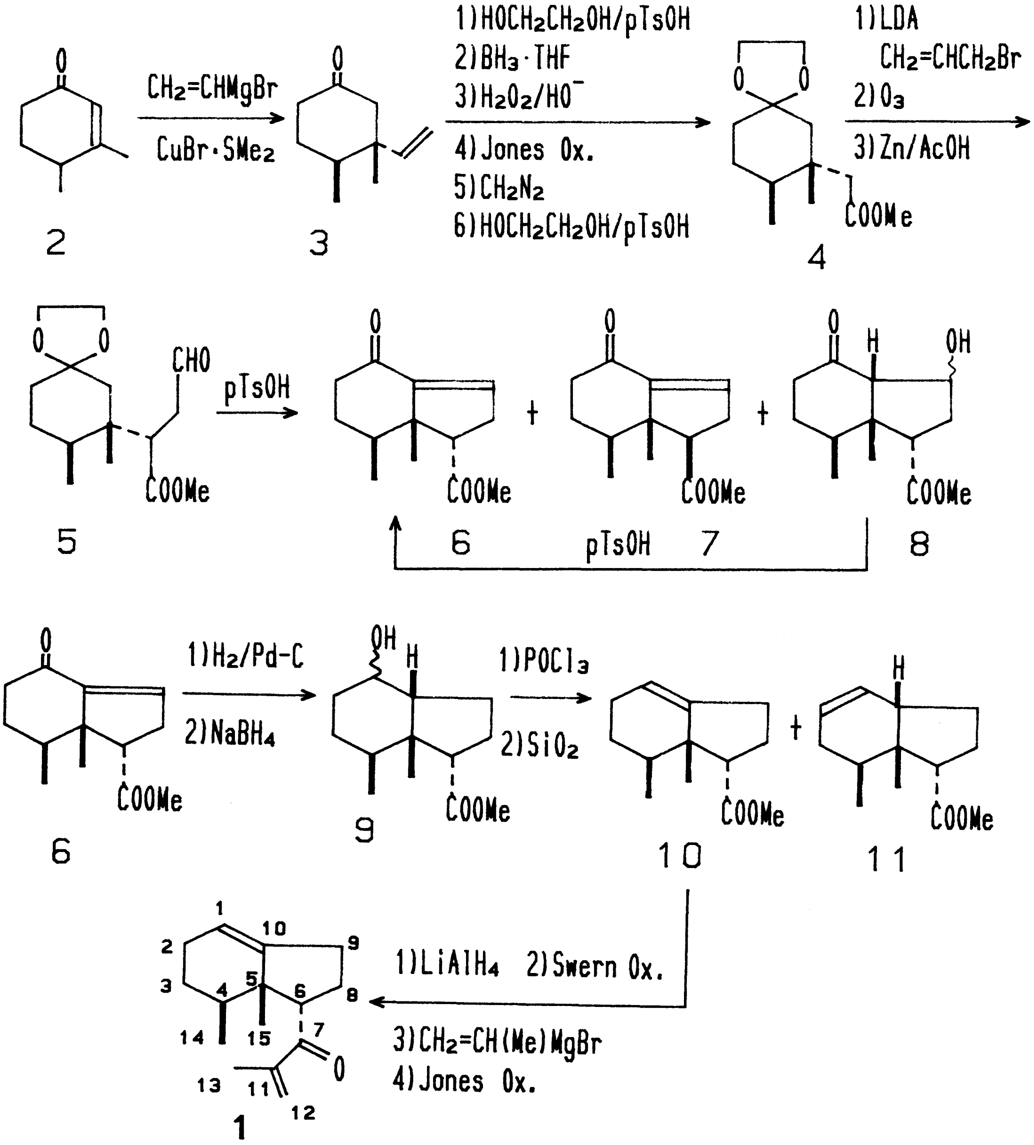
(±)-Chiloscyphone, a sesquiterpene ketone isolated from the liverwort, has been synthesized starting from 3,4-dimethyl-2-cyclohexen-1-one *via* intramolecular aldol condensation.

Chiloscyphone (1) is a sesquiterpene ketone isolated from the liverwort *Chiloscyphus polyanthus* (L.)[1] and the structure was revised recently as depicted in 1 by Connolly and his coworkers.[2] We have developed the new synthetic route[3] to 1 through intramolecular aldol condensation. One of the intermediates could be used for optical resolution and determination of the absolute configuration. We now report the successful synthesis of (±)-chiloscyphone (1).

The cis dimethyl part was obtained by 1,4-addition[4] of the vinyl group to 3,4-dimethyl-2-cyclohexen-1-one (2) in the presence of $CuBr/SMe_2$. Ketal ester 4[5] was derived from 3 in six steps conversion. Alkylation (LDA/allyl bromide) of 4 and ozonolysis (CH_2Cl_2/-78°C) followed by Zn/AcOH treatment afforded ketal aldehyde 5 in a good yield. When 5 was subjected to acidic conditions (pTsOH/acetone-H_2O), three products (6,[5] 7,[5] and 8[5]) were isolated in 35, 23, and 22% yield, respectively. Compound 6 showed the presence of the β proton of the α, β-unsaturated ketone system [δ 6.54 (dd, J=3.3 and 2.1 Hz)], two methyl groups [δ 1.02 (d, J=3.4 Hz) and 1.07 (s)] and methoxycarbonyl group [δ 3.67 (s)] in its ^{1}H NMR spectrum. The spectral data of compound 7 also suggested the similar structure to 6, indicating that these two are isomers in each other concerning the 6-position. When the methyl group at either C-4 or C-5 of 6 was irradiated, NOE's into H-6 were observed. While irradiation at H-6 of 7 caused NOE into H-4. These experiments indicated the orientation of the methoxycarbonyl group as depicted in the formulae. The third compound 8 [IR 3450 cm^{-1}, δ 9.83 (s)] was obviously hydrogen bonded ketol. Since 8 was converted to 6 under the same reaction conditions, the orientation of methoxycarbonyl group was determined to be trans to both methyl groups.

The conversion of enone 6 to olefin 10 was accomplished in three steps. Hydrogenation of enone 6 (H_2/Pd-C) followed by $NaBH_4$ reduction afforded two isomeric alcohols 9, which were dehydrated ($POCl_3$/Py) to give a mixture of trisubstituted olefin 10 [δ 5.39 (1H, m)] and disubstituted olefin 11 [δ 5.61 (2H, m)]. This mixture was separated by $AgNO_3$ impregnated silica-gel column chromatography. The olefin 10 was reduced ($LiAlH_4$), oxidized (Swern oxidation), alkylated [CH_2=C(Me)MgBr], and oxidized (Jones oxidation) to afford 1.[6]

Optical resolution of 9 should be possible and the absolute configuration could be determined by conversion to the corresponding ketone. The work along these lines is under way.



References

1) S. Hayashi, A. Matsuo, and T. Matsuura, Tetrahedron Lett., 1969, 1599; A. Matsuo, Tetrahedron, 28, 1203 (1972).

2) J. D. Connolly, L. J. Harrison, and D. S. Rycroft, J. Chem. Soc., Chem. Commun., 1982, 1236.

3) K. -G. Gerling and H. Wolf, Tetrahedron Lett., 26, 1293 (1985).

4) F. E. Ziegler and P. A. Wender, Tetrahedron Lett., 1974, 449.

5) All compounds show satisfactory spectral and analytical data.

6) The spectral data of the synthetic compound were identical with those reported in Ref. 1.

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