Communications to the Editor

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SYNTHESIS OF dl-6-PROTOILLUDENE

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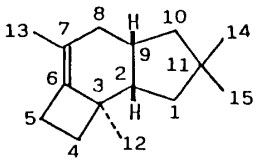
Synthesis of 6-protoilludene (1), a hydrocarbon obtained from mycelia of Fomitopsis insularis and Omphalotus olearius, is described.

KEYWORDS———6-protoilludene; Basidiomycete;sesquiterpene; dehydration reagent; biosynthetic intermediate

6-Protoilludene (1) was isolated from the two species of Basidiomycetes[1] Fomitopsis insularis and Omphalotus olearius, the latter of which produces the sesquiterpenic metabolites illudin-M and -S. This hydrocarbon 1 has been postulated[1] as a hypothetical intermediate in the biosynthesis of humulene-derived sesquiterpenes such as illudol, illudin-M, -S, marasmic acid and so on.[2] Our interest in the intermediary role of 1 in the biosynthesis of the above described sesquiterpenes led us to the study of the synthesis of this hydrocarbon. This paper describes the first synthesis of dl-1 through the sequence which could also be utilized to prepare a substrate for feeding experiments by labeling at the C-7 methyl group.



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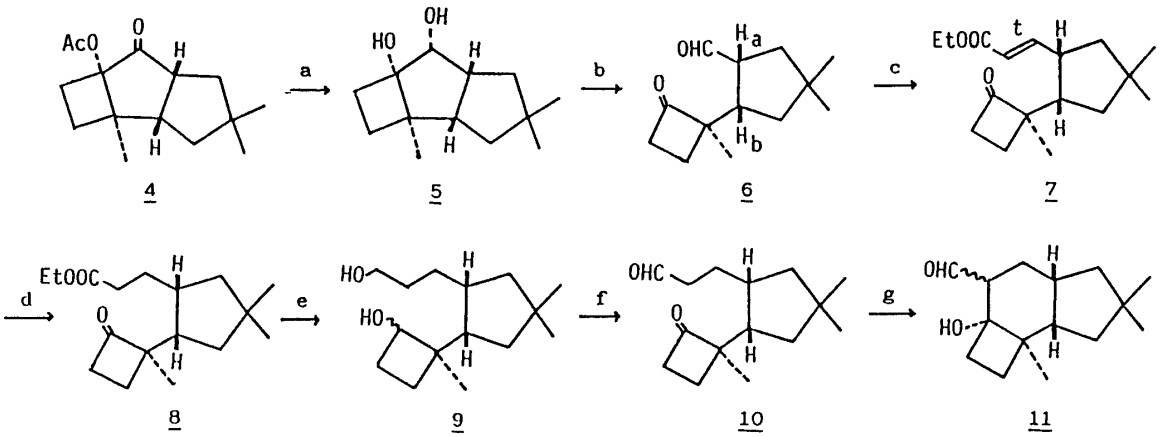
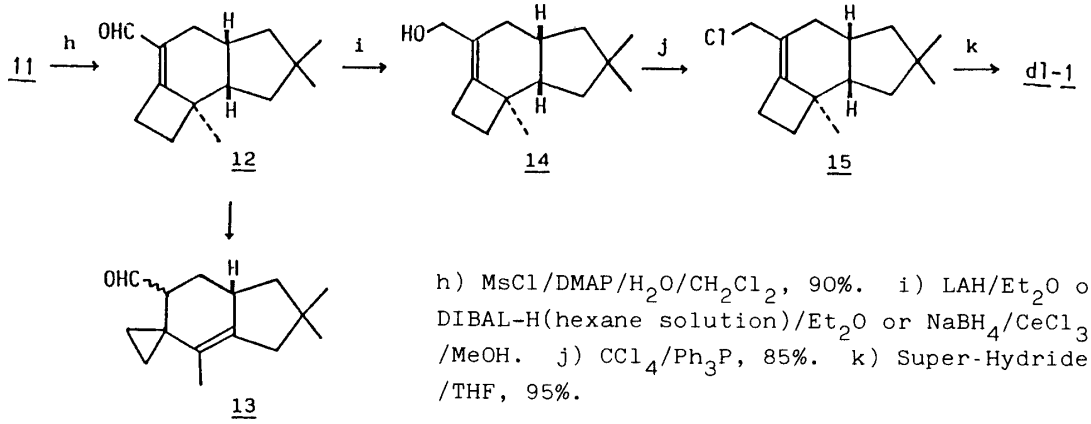
The synthesis was tried according to the route to illudol developed by Matsumoto et al.,[3] but the key intermediate, 8-oxoprotoilludene, proved to cause facile epimerization at C-9.[4] Synthesis of 1 was succeeded by an alternative route[5] which did not involve 8-oxo derivatives.

The ketoacetate 4[4] was reduced with DIBAL-H to give the diol 5 in 80% yield. The diol 5 was oxidized with $NaIO_4$ in DME-H_2O to give the ketoaldehyde 6 in 80% yield. Two carbon homologation of 6 yielding 10 was carried out in the following 4 steps: 1) the Wittig reaction with carbethoxymethylenetriphenylphosphorane, (90%). 2) catalytic hydrogenation with Pd-C in MeOH (quantitative yield), 3) $LiAlH_4$ reduction (90%), 4) the Swern oxidation[6] (70%). The ketoaldehyde 10 was cyclized to 11 by aldol condensation with 5% KOH-MeOH. The ^1H-NMR spectrum showed that the aldol 11 was an epimeric mixture at C-7 (3:1).



a) DIBAL-H(hexane solution)/Et_2O, 80%. b) $NaIO_4$/DME-H_2O, 80%.
c) Ph_3P=CHCOOEt/CH_2Cl_2, 90%. d) H_2/Pd-C/MeOH, quant. e) LAH/Et_2O, 90%.
f) i) DMSO/$(COCl)_2$/CH_2Cl_2, ii) Et_3N, 70%. g) KOH(5%)/MeOH, 80%.

Dehydration of 11 to 12 was a critical step in the synthesis. Several reagents, i.e., KOH/MeOH, p-TsOH, HCl, Al_2O_3/pyridine, MsCl/pyridine (105°C)[4] and MsCl/DMAP, were tried only to get poor yields of 12. A satisfactory result was obtained by using a mixture of MsCl/DMAP/H_2O in CH_2Cl_2 solution[7] for the dehydration step. Treatment of 11 (1.0 mmol) with the dehydration reagent (2.0 ml) (prepared by mixing MsCl (1.15g, 10 mmol), DMAP (610 mg, 5 mmol) and H_2O (72 mg, 4 mmol) in CH_2Cl_2 (13 ml)) overnight at room temperature, gave the dehydrated product 12 in 90% yield. When the reaction was continued for a longer period of time, the enal 12 was gradually transformed to a compound with an illudane carbon skeleton 13 by a cyclobutyl-cyclopropylcarbinyl cation rearrangement. The ^{1}H-NMR spectrum of 13 showed that the product was an epimeric mixture at C-7 (3:1).



h) MsCl/DMAP/H_2O/CH_2Cl_2, 90%. i) LAH/Et_2O or DIBAL-H(hexane solution)/Et_2O or $NaBH_4$/$CeCl_3$/MeOH. j) CCl_4/Ph_3P, 85%. k) Super-Hydride/THF, 95%.

Reduction of the α,β-unsaturated aldehyde 12 with $LiAlH_4$, DIBAL-H or $NaBH_4$-$CeCl_3$[8] gave alcohol 14 which was treated with CCl_4-Ph_3P[9] to yield the chloride 15 in 85% yield. Finally, Super-Hydride reduction[10] of 15 furnished dl-1 in 95% yield. The product thus obtained showed spectral data (MS, ^{1}H-NMR) and gas chromatographic behavior (OV-1 and OV-17, 0.28 mm i.d., 30 m), identical with those of 1 isolated from O. olearius and F. insularis.

The ^{1}H-NMR data (400 MHz, in $CDCl_3$) and the ^{13}C-NMR data (100 MHz, in $CDCl_3$) of 1 are shown in Table I and II.

In the present synthetic route, C-7 methyl group of 1 can be labeled with deuterium or tritium using the correspondingly labeled hydride reagents.

Table I. ^{1}H-NMR Data of 1

H	Chemical shift δ (ppm)	Coupling constant J_{HH}(Hz)
1α	1.29	11, 11.5
1β	1.35	1.8, 8, 11.5
2	2.16	8, 11, 11.2
4	1.75	9, 9, 10.5
4	1.81	3.5, 9, 10.5
5	2.53	3.5, 9, 15
5	2.72	9, 9, 15
8α	1.65(br)	11, 14
8β	1.85	6.5, 14
9	2.34	6.5, 7.5, 11, 11, 11.2
10α	0.96(br)	11, 12.5
10β	1.54	1.8, 7.5, 12.5
12(Me)	0.93	
13(Me)	1.57	
14(Me)	1.05	
15(Me)	1.06	

Table II. ^{13}C-NMR Data of 1

C	Chemical shift δ (ppm)
1	41.4
2	47.2
3	45.8
4	36.9
5	25.5
6	123.1
7	141.8
8	34.2
9	40.7
10	48.7
11	39.2
12	20.5
13	17.3
14	27.5
15	29.9

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4) N. Morisaki, J. Furukawa, H. Kobayashi, S. Iwasaki, A. Itai, S. Nozoe and S. Okuda, Chem. Pharm. Bull., submitted.
5) Physical properties of intermediates.
5: mp 97-98°C (benzene), ^{1}H-NMR($CDCl_3$)δ:0.97(3H, s), 1.05(3H, s), 1.06(3H, s), 3.65(d, J=6 Hz), 2.80(1H, m), 2.32(1H, m).
6: ^{1}H-NMR($CDCl_3$)δ:1.04(3H, s), 1.17(3H, s), 1.36(3H, s), 2.59(ddd, J=8, 9, 12 Hz, H_b), 2.99(ddd, J=5, 8, 9 Hz, H_a), J_{HaHb}=8Hz, 9.78(d, J=4 Hz), IR($CHCl_3$) :1713, 1773 cm^{-1}, MS m/z:180(M-28), 165(M-28-15).
7: ^{1}H-NMR($CDCl_3$)δ:1.02(3H, s), 1.13(3H, s), 1.24(3H, s), 1.28(3H, t, J=7 Hz), 4.19(2H, q, J=7 Hz), 5.76(d, J=16 Hz), 6.95(dd, J=12,16 Hz).

8: ^{1}H-NMR($CDCl_3$)δ:0.98(3H, s), 1.10(3H, s), 1.31(3H, s), 1.26(3H, t, J=7 Hz), 4.13(2H, q, J=7 Hz); MS m/z:280(M^+), 265(M-15), 262, 252.

9: ^{1}H-NMR($CDCl_3$)δ:0.99(3H, s), 1.09(3H, s), 1.14(3H, s), 3.63(2H, m), 4.01-(1H, dd, J=8, 8 Hz).

10: ^{1}H-NMR($CDCl_3$)δ:0.99(3H, s), 1.10(3H, s), 1.31(3H, s), 9.8(bs); MS m/z:236(M^+), 221(M-15), 218, 208, 192.

11(major isomer): ^{1}H-NMR($CDCl_3$)δ:0.89(3H, s), 1.03(3H, s), 1.15(3H, s), 9.88-(1H, bs); MS m/z:221(M-15), 218(M-18), 208.

11(minor isomer): ^{1}H-NMR($CDCl_3$)δ:0.95(3H, s), 1.06(3H, s), 1.15(3H, s), 9.82-(1H, bs).

12: ^{1}H-NMR($CDCl_3$)δ:0.94(3H, s), 1.07(3H, s), 1.21(3H, s), 9.66(1H, s).

13(major isomer): ^{1}H-NMR($CDCl_3$)δ:0.99(3H, s), 1.07(3H, s), 1.29(3H, s), 9.82-(1H, bs), 0.35-0.82(4H, m).

14: ^{1}H-NMR($CDCl_3$)δ:0.94(3H, s), 1.05(3H, s), 1.09(3H, s), 1.31(1H, dd, J=11, 12.5 Hz, H-1α), 1.37(1H, dd, J=8, 12.5 Hz, H-1β), 2.20(1H, ddd, J=8, 11, 11 Hz, H-2), 1.81(1H, ddd, J=9, 9, 10 Hz, H-4), 1.86(1H, ddd, 3.5, 9.5, 10 Hz, H-4), 2.66(1H, ddd, 3.5, 9, 15 Hz, H-5), 2.83(1H, ddd, 9, 9.5, 15 Hz, H-5), 1.61(1H, br.dd, 11, 14.5 Hz, H-8α), 2.13(1H, dd, J=6.5, 14.5 Hz, H-8β), 2.35(1H, ddddd, 6.5, 7, 11, 11, 11 Hz, H-9), 1.00(1H, dd, J=11, 12 Hz, H-10α), 1.58(1H, dd, 7, 12 Hz, H-10β), 4.05(2H, s, H-13); MS m/z:220(M^+), 205(M-15), 202(M-18), 191.

15: ^{1}H-NMR($CDCl_3$-CCl_4)δ:0.94(3H, s), 1.06(3H, s), 1.10(3H, s), 1.30(1H, dd, J=10.5, 11.5 Hz, H-1α), 1.37(1H, dd, J=8.5, 11.5 Hz, H-1β), 2.20(1H, ddd, J=8.5, 10.5, 11 Hz, H-2), 1.82(1H, ddd, J=8.5, 9, 9.5 Hz, H-4), 1.88(1H, ddd, 3.5, 9.5, 9.5 Hz, H-4), 2.67(1H, ddd, 3.5, 8.5 Hz, H-5), 2.80(1H, ddd, 9, 9.5 Hz, H-5), 1.61(1H, br.dd, J=11, 14.5 Hz, H-8α), 2.18(1H, dd, J=7, 14.5 Hz, H-8β), 2.37(1H, ddddd, J=7, 7, 10.5, 11, 11 Hz, H-9), 1.00(1H, dd, J=10.2, 12 Hz, H-10α), 1.58(1H, dd, J=7, 12 Hz, H-10β), 3.90(1H, d, J=11 Hz, H-13), 3.98(1H, d, J=11 Hz, H-13); MS m/z:240 and 238(M^+), 225 and 223(M-15), 202(M-HCl).

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7) The dehydrating reagent was prepared as follows; MsCl (1.15 g, 10 mmol, excess), DMAP (610 mg, 5 mmol) and H_2O (72 mg, 4 mmol) in CH_2Cl_2 (13 ml) was stirred for 2-3 days at room temperature. Crystals initially formed were dissolved during the stirring and the resulting acidic solution proved to be an effective dehydrating reagent for 11. The H_2O, which hydrolyzed MsCl to give MsOH and HCl, was essential for the dehydration and the amount of H_2O should be slightly more than a half mole of DMAP. The ^{1}H-NMR spectrum showed the solution contains MsOH (4 mmol), HCl (4 mmol) and DMAP (5 mmol) in CH_2Cl_2 (13 ml). The reagent was effective even after 6 months.
The mixture of MsOH (8 mmol) and DMAP (5 mmol) in CH_2Cl_2 (13 ml) was not as effective as the reagent described above. The reaction rate was slow, the yield of 12 was lower and 12 was easily transformed to 13 in the reaction mixture.

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