CHEMISTRY LETTERS, pp. 929-932, 1973. Published by the Chemical Society of Japan

SYNTHESIS OF (±)-TETRAHYDROLIGULARENOLIDE

Tochiro TATEE and Takeyoshi TAKAHASHI
Department of Chemistry, Faculty of Science,
The University of Tokyo, Bunkyo-ku, Tokyo 113

The synthesis of (±)-tetrahydroligularenolide [(±)-II] is described to confirm the structure of ligularenolide (I).

The structure and absolute configuration of ligularenolide, a sesquiterpene lactone isolated from "San-Shion" (mountain Shion : root of a Ligularia species), have been shown to be I,[1,2] which on hydrogenation over palladium-charcoal in ethanol yielded tetrahydroligularenolide (II).[1] The total syntheses of some eremophilane sesquiterpenes containing an α,β-unsaturated γ-lactone moiety, (±)-eremophilenolide [(±)-III],[3,4] (±)-3α-hydroxyeremophilenolide [(±)-IV],[5] and (±)-3β-hydroxyeremophilenolide [(±)-V],[5] have been reported. We now wish to describe a synthesis of (±)-tetrahydroligularenolide [(±)-II] belonging to a 10-epi-eremophilane series. This confirms the structure (I) for ligularenolide.

The tetrahydropyranyloxy-trans-decalone (VI)[6,7] was converted into the cyclic acetal (VII), an oil, M^+ at m/e 226 ($C_{13}H_{22}O_3$), ν_{OH} (liquid film) ~3430 cm^{-1}, in the usual manner ($HOCH_2CH_2OH$, TsOH, in PhH) with concomitant hydrolysis of tetrahydropyranyl group. Oxidation of VII with CrO_3 in pyridine gave the known ketone (VIII),[8,9] which was treated with CH_3MgI in ether to give the crude alcohol (IX), an oil, ν_{OH} (liquid film) ~3450 cm^{-1}. This was then subjected to dehydration with $POCl_3$-phosphoric acid in pyridine at 60° to give an olefin mixture, an oil [X[10] and XI (2 : 1) ; by PMR spectral analysis], deacetalization of which followed by catalytic hydrogenation in AcOH in the presence of palladium-charcoal gave the dimethyl-decalone (XII),[11,12] an oil, M^+ at m/e 180 ($C_{12}H_{20}O$), $\nu_{C=O}$ (liquid film) 1715 cm^{-1}, PMR ($CDCl_3$) : δ 0.86 (unresolved multiplet, s-Me) and 0.92 (s, t-Me)(yield from VI : 16 %).

Carbomethoxylation of XII with NaH and dimethyl carbonate in dioxane under nitrogen gave a mixture of β-keto-esters, which was separated by silica gel column chromatography to afford XIII (y : 75 %)[13] and XIV (y : 12 %)[14]. The structure of XIV was deduced from PMR spectral data which showed a doublet (J = 12 Hz) due to an axial(β)-proton at C-9 coupled with the ring juncture proton.

As model experiments of the alkylation of XIII, alkylation of α-carbomethoxycyclohexanone with ethyl α-halogenopropionate in the presence of NaH (or KH) under nitrogen was examined.[15] The ratio of C-alkylated (XV)[16] and O-alkylated (XVI)[16] products varied also with the solvents used (Table 1). The best yield of C-alkylated product (XV) was obtained with NaH - MeCHICOOEt - PhH.

Table 1

Hydrides	Halides	Solvents	Products in ratio* XV	XVI
NaH	MeCHBrCOOEt	PhH**	70	30
NaH	MeCHICOOEt	PhH	85	15
KH	MeCHBrCOOEt	PhH	50	50
KH	MeCHICOOEt	PhH	74	26
NaH	MeCHBrCOOEt	DMSO***	68	32
NaH	MeCHICOOEt	DMSO	76	24
KH	MeCHBrCOOEt	DMSO	29	71
KH	MeCHICOOEt	DMSO	73	27

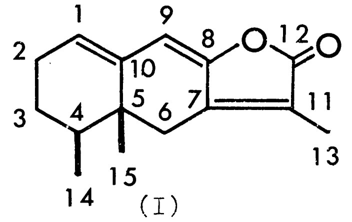
* Determined by GLC.

** Under reflux for 18 ~ 29 h.

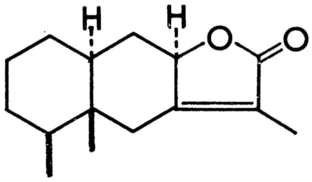
*** At room temperature for 17 ~ 24 h.

Alkylation of XIII in PhH with ethyl α-iodopropionate in the presence of NaH under nitrogen gave the product showing three spots on TLC. The product corresponding to the least polar spot (y : ca. 30 %) was separated by silica gel column chromatography to give the C-alkylated product (XVII),[17] which was shown to be a diastereomeric mixture by the PMR spectrum.[17] Compounds corresponding to the other two spots were the diastereomeric O-alkylated products (XVIII ; y : 26 %),[18] which were separated by silica gel column chromatography. When ethyl α-bromopropionate was used as alkylating reagent with NaH in PhH, only a small amount of XVII was obtained ; the predominant product was XVIII.

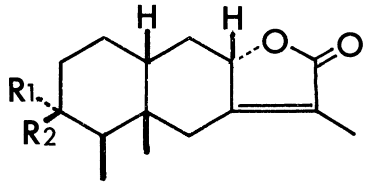
The C-alkylated compound (XVII) was treated with hydrochloric acid - AcOH under reflux to afford in a single step (±)-tetrahydroligularenolide [(±)-II], m.p. 83-84° (y : 57 %). This substance showed IR, PMR, and MS spectra identical with those of the authentic tetrahydroligularenolide[1] obtained from natural ligularenolide. Thus, the structure (I) was confirmed for ligularenolide.



(I)



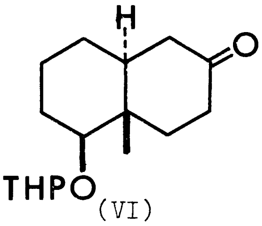
(II)



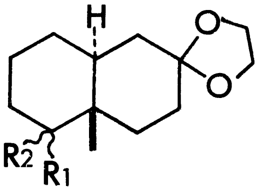
(III) R_1 = H, R_2 = H

(IV) R_1 = OH, R_2 = H

(V) R_1 = H, R_2 = OH

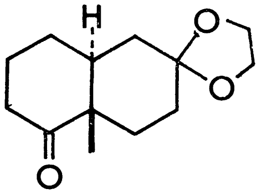


(VI)

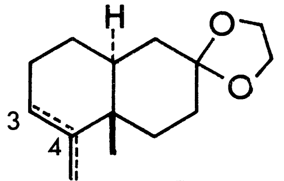


(VII) R_1 = β-OH, R_2 = α-H

(IX) R_1 = Me, R_2 = OH

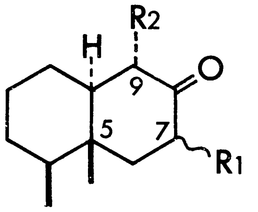


(VIII)



(X) Δ^3

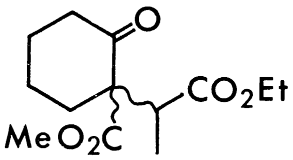
(XI) $\Delta^{4(14)}$



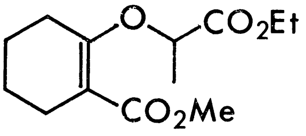
(XII) R_1 = H, R_2 = H

(XIII) R_1 = CO_2Me, R_2 = H

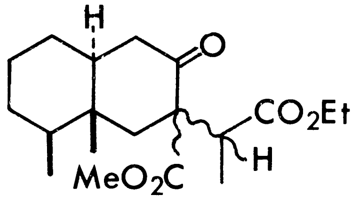
(XIV) R_1 = H, R_2 = CO_2Me



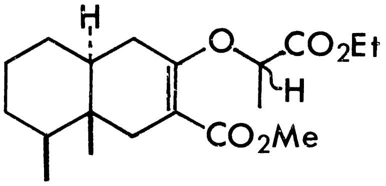
(XV)



(XVI)



(XVII)



(XVIII)

REFERENCES

1) Y.Tanahashi, Y.Ishizaki, T.Takahashi, and K.Tori, Tetrahedron Lett., 1968, 3739 ; Y.Ishizaki, Y.Tanahashi, T.Takahashi, and K.Tori, Tetrahedron, 26, 5387 (1970).

2) The numbering shown in I is that employed for eremophilane-type sesquiterpenes. The same numbering was used for decalin derivatives reported here for

convenience.

3) E.Piers, M.B.Geraghty, and R.D.Smillie, Chem. Commun., 1971, 614.

4) I.Nagakura, H.Ogata, S.Yokomori, S.Maeda, and Y.Kitahara, 15th Symposium on the Chemistry of Natural Products, Nagoya, 1971, Symposium papers, p.239. Cf. C. Kabuto, N.Takada, S.Maeda, and Y.Kitahara, Chem. Lett., 1973, 371.

5) S.Maeda, I.Nagakura, M.Funamizu, and Y.Kitahara, 28th Annual Meeting of the Chemical Society of Japan, Tokyo, 1973, Abstract papers, III, p.1793.

6) R.H.Jaeger, Tetrahedron, 2, 326 (1958).

7) Compounds (VI ~ XVIII) utilized for the synthesis are racemic modifications.

8) R.F.Church, R.E.Ireland, and D.R.Shridhar, J. Org. Chem., 27, 707 (1962).

9) R.E.Ireland, S.W.Baldwin, and S.C.Welch, J. Amer. Chem. Soc., 94, 2056 (1972).

10) Ireland et al. (ref. 9) obtained an olefin ketal (X) by treatment of VIII with MeLi followed by dehydration with I_2 at 140°.

11) Only *one* racemic modification (XII) was obtained ; the *cis* relationship of the two methyl groups was deduced from the identification of the synthetic (±)-II as (±)-tetrahydroligularenolide.

12) The synthesis of XII via other routes had been described : a) L.H.Zalkow, F.X. Markley, and C.Djerassi, J. Amer. Chem. Soc., 82, 6354 (1960). b) A.R.Pinder and A.K.Torrence, J. Chem. Soc. (C), 1971, 3410. c) E.Piers, R.W.Britton, and W. de Waal, Can. J. Chem., 47, 4307 (1969). See also, d) C.Berger, M.Franck-Neumann, and G.Ourisson, Tetrahedron Lett., 1968, 3451.

13) XIII had been obtained as a sole product on carbomethoxylation of XII in dry PhH (ref. 12).

14) m.p. 87-88°, M$^+$ at m/e 238 ($C_{14}H_{22}O_3$); IR (nujol): 1740, 1715 cm^{-1}; UV (EtOH): λ_{max} 258 nm (ε 130); PMR ($CDCl_3$): δ 0.89 (m, s-Me), 0.97 (s, t-Me), 3.27 (d, J = 12 Hz, proton at C-9), 3.74 (s, -COOMe).

15) Cf. S.J.Rhoads and R.W.Hasbrouck, Tetrahedron, 22, 3557 (1966) ; D.M.Pond and R.L.Cargill, J. Org. Chem., 32, 4064 (1967) ; A.Chatterjee, D.Banerjee, and S. Banerjee, Tetrahedron Lett., 1965, 3851. See also ref. 3.

16) Spectral data of XV and XVI were compatible with the structures XV and XVI, respectively.

17) An oil, M$^+$ at m/e 338 ($C_{19}H_{30}O_5$); IR (liquid film): 1740, 1720 cm^{-1}; PMR (C_6D_6): δ 0.78 (s, t-Me), 0.80 (m, s-Me), 1.03 (t, J = 7 Hz, $-COOCH_2C\underline{H}_3$), 1.33 (d, J = 7 Hz, $C\underline{H}_3$-CH-COOEt), 3.29 (s, -COOMe), 3.32 (quartet, J = 7 Hz, CH_3-C$\underline{H}$-COOEt), 4.02 (quartet, J = 7 Hz, $-COOC\underline{H}_2CH_3$), 4.04 (quartet, J = 7 Hz, $-COOC\underline{H}_2CH_3$, the other diastereomer).

18) *Less polar diastereomer*. An oil, M$^+$ at m/e 338 ($C_{19}H_{30}O_5$); IR (liquid film): 1750~1730, 1715, 1635 cm^{-1}; UV (EtOH): λ_{max} 245 nm (ε 4800); PMR (C_6D_6): δ 0.64 (s, t-Me), 0.77 (m, s-Me), 0.94 (t, J = 7 Hz, $-COOCH_2C\underline{H}_3$), 1.53 (d, J = 7 Hz, $C\underline{H}_3$-CH-COOEt), 3.50 (s, -COOMe), 3.93 (q, J = 7 Hz, $-COOC\underline{H}_2CH_3$), 4.66 [q, J = 7 Hz, -O-C$\underline{H}$(CH_3)(COOEt)]. *More polar diastereomer*. An oil, M$^+$ at m/e 338 ($C_{19}H_{30}O_5$); IR (liquid film): 1755, 1730, 1700, 1640 cm^{-1}; UV (EtOH): λ_{max} 247 nm (ε 12000) ; PMR (C_6D_6): δ 0.63 (s, t-Me), 0.77 (m, s-Me), 0.97 (t, J = 7 Hz, $-COOCH_2C\underline{H}_3$), 1.47 (d, J = 7 Hz, $C\underline{H}_3$-CH-COOEt), 3.51 (s, -COOMe), 3.94 (q, J = 7 Hz, $-COOC\underline{H}_2CH_3$), 4.46 [q, J = 7 Hz, -O-C$\underline{H}$(CH_3)(COOEt)].

(Received July 12, 1973)