Total Synthesis of (±)-Tetrahydroligularenolide[1)]

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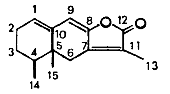
A total synthesis of (±)-tetrahydroligularenolide [(±)-**2**] is described. 10β-Methyl-5β-tetrahydropyranyloxy-*trans*-2-decalone (**6**) was converted in seven steps into 3-methoxycarbonyl-5,10-dimethyl-*trans*-2-decalone (**15**), which on alkylation with ethyl α-iodopropionate gave 3-(1-ethoxycarbonylethyl)-3-methoxycarbonyl-5,10-dimethyl-*trans*-2-decalone (**19**) and 6-(1-ethoxycarbonylethoxy)-7-methoxycarbonyl-1β,8aβ-dimethyl-1,2,3,4,4a,5,8,8a-*trans*-octahydronaphthalene (**20**). Hydrolysis of **19** proceeded with a loss of carbon dioxide to afford (±)-tetrahydroligularenolide [(±)-**2**].

It has been reported that a sesquiterpene lactone, ligularenolide, was isolated from "San-shion"[2)] (the roots of *Ligularia* species), and its structure including an absolute stereochemistry was shown to be **1**,[3)] which on hydrogenation over palladium-charcoal in ethanol gave tetrahydroligularenolide (**2**).[3)] We wish to describe a total synthesis of (±)-tetrahydroligularenolide [(±)-**2**] with a 10-epi-eremophilane skeleton.[1)] Some α,β-unsaturated γ-lactones of eremophilane type, (±)-eremophilenolide [(±)-**3**],[4,5)] (±)-3α-hydroxyeremophilenolide [(±)-**4**][6)] and (±)-3β-hydroxyeremophilenolide [(±)-**5**][6)] have been synthesized. A conversion of (—)-5α,6α-epoxydihydroalantolactone into (—)-**2** has been described.[7)] Recently, a total synthesis of (±)-**2** was reported;[4b)] this synthesis includes a final introduction of a methyl group to C-11, while the present communication contains an alkylation by three carbon units and the subsequent lactonization.



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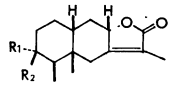
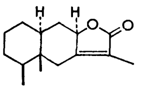


3 R1= H, R2= H
4 R1= OH, R2= H
5 R1= H, R2= OH



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Acetalization of a tetrahydropyranyloxy-*trans*-decalone (**6**)[8,9)] with ethylene glycol in the presence of *p*-toluenesulfonic acid gave a cyclic acetal (**7**) with concomitant hydrolysis of a tetrahydropyranyl group. The alcohol (**7**) was oxidized with chromium trioxide in pyridine to afford the known ketone (**8**),[10)] which was then treated with methyl magnesium iodide in ether to give a crude alcohol (**9**). Dehydration of **9** with phosphorus oxychloride and phosphoric acid in pyridine yielded a mixture of olefins, **10**[11)] and **11** (in a ratio of 2: 1). Deacetalization of the olefin mixture to yield a mixture of **12** and **13**, and the subsequent hydrogenation in acetic acid in the presence of palladium-charcoal gave a dimethyldecalone (**14**)[12)] (yield from **6**: 16%). Only one stereoisomer (**14**) was obtained; a *cis* relationship of the two methyl groups could be derived after completion of the synthesis of (±)-**2**.

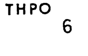
Pinder and Torrence[12c)] described a methoxycarbonylation of **14** with dimethyl carbonate and sodium hydride in dry benzene under a nitrogen atmosphere to yield **15** as the sole product. A similar treatment of **14** in dioxane gave a mixture of β-keto-esters, which was subjected to separation by silica gel chromatography to afford **15**[12c)] (y: 75%) and **16** (y: 12%). The PMR spectrum of **16** showed a doublet (*J*= 12 Hz) at δ 3.27 due to an axial (β)-proton coupled with a ring juncture proton; the structure **16** was therefore shown for the latter ester.

As a model experiment of alkylation of **15**, α-methoxycarbonylcyclohexanone was alkylated[13)] with ethyl α-halogenopropionate in the presence of sodium hydride (or potassium hydride) under a nitrogen atmosphere. *C*-alkylated (**17**) and *O*-alkylated (**18**) products were

TABLE 1. ALKYLATION OF α-METHOXYCARBONYLCYCLOHEXANONE

Halides	Hydrides	Solvents	Products in ratio[a)] 17	Products in ratio[a)] 18	Yield (%) (17+18)
$CH_3CHBrCOOC_2H_5$	NaH	PhH[b)]	70	30	73
$CH_3CHBrCOOC_2H_5$	KH	PhH	50	50	64
$CH_3CHICOOC_2H_5$	NaH	PhH	85	15	66
$CH_3CHICOOC_2H_5$	KH	PhH	74	26	57
$CH_3CHBrCOOC_2H_5$	NaH	DMSO[c)]	68	32	77
$CH_3CHBrCOOC_2H_5$	KH	DMSO	29	71	82
$CH_3CHICOOC_2H_5$	NaH	DMSO	76	24	64
$CH_3CHICOOC_2H_5$	KH	DMSO	73	27	42

a) Determined by glc. b) Under reflux for 18—29 hr.
c) At room temperature for 17—24 hr.



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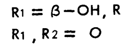
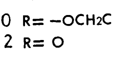
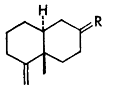


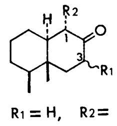
7 R_1 = β−OH, R_2 =α−H
8 R_1, R_2 = O
9 R_1 = CH_3, R_2 = OH



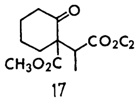
10 R= $-OCH_2CH_2O-$
12 R= O



11 R = $-OCH_2CH_2O-$
13 R = O



14 R_1 = H, R_2 = H
15 R_1 = CO_2CH_3, R_2 = H
16 R_1 = H, R_2 = CO_2CH_3



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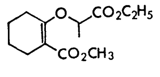

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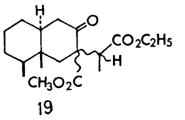

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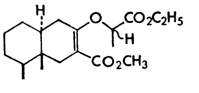

20a and 20b

obtained in the ratio listed in Table 1. When the reaction was carried out with ethyl α-iodopropionate, sodium hydride and benzene, the best yield of **17** was obtained.

The keto-ester (**15**) in benzene was alkylated with ethyl α-iodopropionate in the presence of sodium hydride under a nitrogen atmosphere. The resulting product showed three spots on tlc, and was subjected to separation by silica gel chromatography to give the *C*-alkylated (**19**; y: 30%) and the *O*-alkylated (**20a** and **20b**; y: 26%) products. The former substance (**19**) corresponding to the least polar spot was found to be a diastereomeric mixture by its PMR spectrum. The latter products (**20a** and **20b**) proved to be a diastereomeric mixture corresponding to the other two spots, and was subjected to further separation on a column of silica gel to give each diastereomer. Alkylation of **15** in benzene with ethyl α-bromopropionate and sodium hydride resulted in formation of a small amount of **19**, the *O*-alkylated products (**20a** and **20b**) were obtained as predominant products.

Hydrolysis of **19** with hydrochloric acid in acetic acid under reflux was effected with a loss of carbon dioxide to afford (±)-**2** (y: 57%), which was found to be the same (except optical rotational data) as (−)-tetrahydroligularenolide (**2**)[3] derived from natural (−)-ligularenolide (**1**).

Experimental

IR spectra were measured with a Hitachi EPI-G2 spectrometer, UV spectra with a Hitachi EPS-3 spectrometer, and mass spectra with a Hitachi RMU-6-Tokugata mass spectrometer with use of an indirect system operating at 70 eV. PMR spectra were measured with a JEOL JNM PS-100 (100 MHz), a JEOL JNM 3H-60 (60 MHz), a Hitachi R-20 (60 MHz) or a Hitachi R-24 (60 MHz) spectrometer. Chemical shifts were expressed in terms of δ downfield from TMS as an internal standard, and coupling constants in Hz. Gas chromatographic (glc) analyses were carried out on a Shimadzu gas chromatograph model GC-4APF. Thin layer chromatography (tlc) was carried out on Kieselgel G (E. Merck). Wakogel C-200 (Wako Pure Chemical Co.) was used for column chromatography. Melting points were determined on a hot block and are uncorrected.

*2,2-Ethylenedioxy-5β-hydroxy-10β-methyl-*trans*-decalin (7).* 10β-Methyl-5β-tetrahydropyranyloxy-*trans*-2-decalone (**6**; 5.6 g)[8,9] was dissolved in a mixture of benzene (200 ml) containing *p*-toluenesulfonic acid (120 mg) and ethylene glycol (3 ml), and the mixture was refluxed under a Dean-Stark water separator for 16 hr. The cooled solution was poured into a 5% aqueous potassium hydrogen carbonate solution, and then extracted with ether. The organic layer was washed with brine and dried over magnesium sulfate. The solvent was removed and the residue was chromatographed on a column of silica gel (300 g). Elution with a mixture of benzene and ether (9: 1) and removal of the solvents afforded an oil (**7**[10]; 3.6 g; y: 76%), IR (liquid) 3430 cm^{-1}; PMR ($CDCl_3$) δ 0.86 (3H, s; *t*-CH_3) and 3.96 (4H, s; $-OCH_2CH_2O-$); MS *m/e* 226 [M^+ ($C_{13}H_{22}O_3$); relative intensity, 4%] and *m/e* 99 (100%).

*6,6-Ethylenedioxy-9-methyl-*trans*-1-decalone (8).* A solution of chromium trioxide (9 g) in pyridine (90 ml) was added to a solution of **7** (3.6 g) in pyridine (90 ml), and the resulting solution was allowed to stand at room temperature overnight. Extraction with ether and the usual treatment gave an oil which was chromatographed on a column of silica gel. Elution with a mixture of benzene and ether (5: 1) gave an oil (2.7 g), which on solidification gave **8**, mp 44—47 °C (lit,[10a] mp 41—45 °C; lit,[10b] mp 45—47 °C), IR (Nujol) 1715 cm^{-1}; PMR ($CDCl_3$) δ 1.13 (3H, s; *t*-CH_3) and 3.92 (4H, s; $-OCH_2CH_2O-$); MS *m/e* 224 [M^+($C_{13}H_{20}O_3$); 4%] and *m/e* 99 (100%).

*2,2-Ethylenedioxy-5-hydroxy-5,10-dimethyl-*trans*-decalin (9).* To the Grignard reagent prepared from methyl iodide (25 g) and magnesium (2.5 g) in ether (30 ml) at 0 °C was added a solution of **8** (2.7 g) in ether (40 ml). The reaction mixture was stirred for 2 hr at room temperature, and then decomposed with aqueous ammonium chloride solution. Extraction with ether and the usual work-up gave a residue which was chromatographed on a column of silica gel (160 g). Elution with a mixture of benzene and ether (8: 1) gave a crude alcohol (**9**; 2 g), an oil (one spot on tlc), on removal of the solvents; IR (liquid) 3450 cm^{-1}; PMR ($CDCl_3$) δ 0.91 (3H, s; *t*-CH_3), 1.12 (3H, s; $CH_3\text{–}\overset{|}{\underset{|}{C}}\text{–}OH$), and 3.93 (4H, s; $-OCH_2CH_2O-$).

Dehydration of the Alcohol (9) and Subsequent Deacetalization. Crude alcohol (**9**; 2 g) in pyridine (100 ml) was added dropwise to a solution of phosphorus oxychloride (30 ml) and phosphoric acid (1 ml) in pyridine (60 ml) at 0 °C with stirring, and the mixture was warmed at 55 °C for 20 hr. The cooled mixture was poured into ice water, and the product was extracted with ether. After the usual treatment, a mixture of **10**[10b] and **11** (2: 1) was obtained as an oil (1.2 g); IR (liquid) 3090, 1640, 1375, 1360, 1140, and 1085 cm^{-1}; PMR ($CDCl_3$) δ 0.96 (s; *t*-CH_3 of **10**), 1.02 (s; *t*-CH_3 of **11**), 1.65 (d; *J*=2 Hz; $CH_3\text{–}C{=}C$), 3.94 (s; $-OCH_2CH_2O-$), 4.64 (m; $C{=}CH_2$), and 5.24 (m; $C{=}CH$); MS *m/e* 222 [M^+ ($C_{14}H_{22}O_2$); 2%] and *m/e* 99 (100%) [*cf.* lit,[10b,11] spectral data for pure **10**: bp 90—95 °C/0.04 mmHg, IR ($CHCl_3$) 1375 and 1130—1050 cm^{-1}; PMR ($CDCl_3$) δ 1.02 (s; *t*-CH_3), 1.65 (d, *J*=2 Hz; $CH_3\text{–}C{=}C$), 3.94 (s; $-OCH_2CH_2O-$), and 8.59 (m; $C{=}CH$)]. The signals at δ 0.96 and 1.02 appeared in an integrated intensity ratio of 2: 1.

A mixture of unsaturated cyclic ketals (1.2 g; **10** and **11**) was treated with acetic acid (48 ml) and water (12 ml) at 80 °C for 8 hr. The solvent was removed and the residue was passed through a column of silica gel (70 g) using benzene as an eluent. On removal of the solvent, a mixture of unsaturated ketones (**12** and **13**; 2: 1) was obtained as an oil (677 mg; yield from **7**: 24%)); IR (liquid) 1715 and 1640 cm^{-1}; PMR ($CDCl_3$) δ 1.14 (s; *t*-CH_3 of **12**), 1.18 (s; *t*-CH_3 of **13**), 1.66 (d, *J*=2 Hz; $CH_3\text{–}C{=}C$), 4.59 and 4.65 (each m; $C{=}CH_2$), and 5.25 (m; $C{=}CH$); MS *m/e* 178 [M^+ ($C_{12}H_{18}O$); 55%] and *m/e* 93 (100%). The signals at δ 1.14 and 1.18 appeared in an integrated intensity ratio of 2: 1.

*5β,10β-Dimethyl-*trans*-2-decalone (14).* An olefin mixture (630 mg; **12** and **13**) in acetic acid (20 ml) was hydrogenated in the presence of 10% palladium–charcoal (155 mg) at room temperature for 2 hr. After filtration of the catalyst, the solvent was evaporated to give a residue which was chromatographed on a column of silica gel (30 g). Elution with a mixture of light petroleum and ether (8: 1) and removal of the solvents afforded a dimethyldecalone (**14**; 563 mg; y: 88%) (yield from **6**: 16%) as a sole product, an oil, bp 104—106 °C/2 mmHg, IR (liquid) 1715 cm^{-1}; PMR ($CDCl_3$) δ 0.86 (3H, m; *s*-CH_3) and 0.92 (3H, s; *t*-CH_3); MS *m/e* 180 [M^+($C_{12}H_{20}O$); 27%] and *m/e* 109 (100%) [lit,[12b] bp 83—86 °C/1 mmHg, IR (liquid) 1712 cm^{-1}; PMR ($CDCl_3$) δ 0.87 (m; *s*-CH_3) and 0.92 (s; *t*-CH_3)]. 2,4-Dinitrophenylhydrazone (crystallized from ethanol): mp 157—158 °C. Found: C, 60.04; H, 6.53; N, 15.49%. Calcd for $\mathrm{C_{18}H_{24}N_4O_4}$: C, 59.98; H, 6.71; N, 15.55% [*cf.* lit,[12a)] 2,4-dinitrophenylhydrazone of (+)-**14**: mp 172.5—173.5 °C].

Methoxycarbonylation of the Dimethyldecalone (14). A mixture of the dimethyldecalone (**14**; 137 mg), dimethyl carbonate (1.08 g) and sodium hydride (120 mg of a 50% dispersion in mineral oil) in dioxane (3 ml) was stirred under a nitrogen atmosphere at 80—85 °C for 4 hr. The cooled mixture was treated with acetic acid (1 ml) and then extracted with ether. The extract was washed with water and dried over magnesium sulfate. The solvent was removed and the residue (239 mg) was chromatographed on a column of silica gel (20 g) using the following solvents as eluent: light petroleum (fr 1, 100 ml; frs 2—3, each 30 ml), light petroleum and ether (20: 1) (frs 4—12, each 30 ml), light petroleum and ether (10: 1) (frs 13—18, each 30 ml), and light petroleum and ether (5: 1) (frs 19—21, each 60 ml). Fraction 5 gave a keto-ester (**15**; 136 mg; y: 75%), an oil, bp 149—155 °C/2 mmHg (lit,[12c)] bp 122—125 °C/0.25 mmHg), IR (liquid) 3200—2600, 1750, 1720, 1660, and 1620 cm^{-1}; UV (EtOH) $\lambda_{\max}$ 257 nm (ε 11000); PMR ($\mathrm{CDCl_3}$) δ 0.68 (3H, s; *t*-$\mathrm{CH_3}$), 0.89 (3H, m; *s*-$\mathrm{CH_3}$), 3.76 (3H, s; $\mathrm{-CO_2CH_3}$), and 12.19 (s; enolic proton); MS *m/e* 238 [$\mathrm{M^+(C_{14}H_{22}O_3)}$; 11%] and *m/e* 109 (100%). Fractions 13—14 afforded an isomeric keto-ester (**16**; 21 mg; y: 12%), mp 87—88 °C, IR (Nujol) 1740 and 1715 cm^{-1}; UV (EtOH) $\lambda_{\max}$ 258 nm (ε 130); PMR ($\mathrm{CDCl_3}$) δ 0.89 (3H, m; *s*-$\mathrm{CH_3}$), 0.97 (3H, s; *t*-$\mathrm{CH_3}$), 3.27 (1H, d, J=12 Hz; $\mathrm{-\overset{|}{C}HC\underline{H}(CO_2CH_3)CO-}$), and 3.74 (3H, s; $\mathrm{-CO_2CH_3}$); MS *m/e* 238 [$\mathrm{M^+(C_{14}H_{22}O_3)}$; 4%] and *m/e* 109 (100%). Found: C, 70.26; H, 9.40%. Calcd for $\mathrm{C_{14}H_{22}O_3}$: C, 70.55; H, 9.31%.

Alkylation of α-Methoxycarbonylcyclohexanone. To sodium hydride (910 mg of a 50% dispersion in mineral oil; washed thrice by decantation with dry light petroleum) was added α-methoxycarbonylcyclohexanone (3 g) in dry ether (50 ml) with stirring to give the enolate, which was filtered and washed with ether. Dry dimethyl sulfoxide (50 ml) and then ethyl α-bromopropionate (8 g) were added dropwise to the enolate, and the whole was stirred at room temperature for 19 hr under a nitrogen atmosphere. After addition of water (150 ml), the reaction mixture was extracted with light petroleum. The extract was washed with water, dried over magnesium sulfate and the solvent was removed to give an oil (7.6 g). Gas chromatographic analysis showed that the ratio of the *C*-alkylated (**17**) and the *O*-alkylated (**18**) products was *ca.* 2: 1. A part (326 mg) of the oil was subjected to separation by silica gel (20 g) column chromatography using the following solvents as eluent: light petroleum and ether (20: 1) (frs 1—2, each 50 ml; frs 3—9, each 30 ml), light petroleum and ether (10: 1) (frs 10—12, each 30 ml; frs 13—18, each 20 ml), and light petroleum and ether (5: 1) (frs 19—22, each 85 ml). Fractions 2 and 3 gave ethyl α-bromopropionate and a small amount of the starting material, respectively. From fractions 11—12, the *C*-alkylated product (**17**; 63 mg) was obtained as an oil, IR (liquid) 1750—1715 cm^{-1}; PMR ($\mathrm{CDCl_3}$) δ 1.14 (3H, d, J=7 Hz; $\mathrm{C\underline{H}_3\overset{|}{C}H-}$), 1.26 (3H, t, J=7 Hz; $\mathrm{C\underline{H}_3CH_2-}$), 3.18 (1H, q, J=7 Hz; $\mathrm{CH_3\overset{|}{C}\underline{H}CO_2C_2H_5}$), 3.75 (3H, s; $\mathrm{-CO_2CH_3}$) and 4.13 (2H, q, J=7 Hz; $\mathrm{-CO_2C\underline{H}_2CH_3}$); MS *m/e* 256 [$\mathrm{M^+(C_{13}H_{20}O_5)}$; 4%] and *m/e* 123 (100%). This material (50 mg) was further chromatographed on a column of silica gel (5 g). Elution with a mixture of light petroleum and ether (5: 1) gave the analytical sample. Found: C, 60.76; H, 7.83%. Calcd for $\mathrm{C_{13}H_{20}O_5}$: C, 60.92; H, 7.87%. Glc retention time 10.0 min (column: neopentylglycol succinate, 160 °C, $\mathrm{N_2}$, 85 ml/min) and 9.7 min (column: Diasolid H-523, 160 °C, $\mathrm{N_2}$, 85 ml/min). Fractions 13—15 gave a mixture of **17** and **18** (53 mg). Fractions 16—22 afforded the O-alkylated product (**18**; 47 mg), an oil, IR (liquid) 1760—1720 and 1630 cm^{-1}; PMR ($\mathrm{CDCl_3}$) δ 1.28 (3H, t, J=7 Hz; $\mathrm{C\underline{H}_3CH_2-}$), 1.51 (3H, d, J=7 Hz; $\mathrm{C\underline{H}_3\overset{|}{C}H-}$), 3.70 (3H, s; $\mathrm{-CO_2CH_3}$), 4.18 (2H, q, J=7 Hz; $\mathrm{-CO_2C\underline{H}_2CH_3}$) and 4.56 (1H, q, J=7 Hz; $\mathrm{CH_3\overset{|}{C}\underline{H}CO_2C_2H_5}$); MS *m/e* 256 [$\mathrm{M^+(C_{13}H_{20}O_5)}$; 7%] and *m/e* 124 (100%). The product (49 mg) was further chromatographed on a column of silica gel (5 g). Elution with a mixture of light petroleum and ether (5: 1) gave an analytical sample. Found: C, 60.73; H, 8.05%. Calcd for $\mathrm{C_{13}H_{20}O_5}$: C, 60.92; H, 7.87%. Glc retention time 14.2 min (column: neopentylglycol succinate, 160 °C, $\mathrm{N_2}$, 85 ml/min) and 14.0 min (column: Diasolid H-523, 160 °C, $\mathrm{N_2}$, 85 ml/min). The combined yield of the two alkylated products (**17** and **18**) was 77%.

Other experiments under various conditions were performed by similar procedures to those described above. The resulting mixture of products was subjected to analysis by glc; the results are summarized in Table 1.

Alkylation of the Keto-ester (15). (a) Sodium hydride (180 mg of a 50% dispersion in mineral oil), washed by decantation with dry benzene, was suspended in the same solvent (3 ml). The keto-ester (**15**; 190 mg) in dry benzene (6 ml) was added and the mixture was stirred at room temperature for 40 min. Ethyl α-iodopropionate (990 mg) was then added and the resulting mixture was refluxed under a nitrogen atmosphere for 17 hr. The cooled reaction mixture was treated with 1 M hydrochloric acid (2 ml), and extracted with ether after addition of water. The organic layer was washed with an aqueous sodium bicarbonate solution and water, and dried over magnesium sulfate. Evaporation of the solvents afforded an oil (1.04 g), which showed three spots due to alkylated products on tlc besides those due to ethyl α-iodopropionate and the starting material. The oil was subjected to separation by a column of silica gel (20 g) to give the following fractions: fr 1 [eluted with light petroleum and ether (30: 1); 50 ml], frs 2—4 [light petroleum and ether (20: 1); each 50 ml], frs 5—19 [light petroleum and ether (10: 1); each 15 ml], and frs 20—24 [light petroleum and ether (4: 1); each 30 ml].

Fractions 2—4 gave ethyl α-iodopropionate and a small amount of the starting material (580 mg in total). Fractions 10—16 afforded the *C*-alkylated product (**19**; 80 mg; y: 30%), an oil, IR (liquid) 1740 and 1720 cm^{-1}; PMR ($\mathrm{CDCl_3}$) δ 0.81 (3H, s; *t*-$\mathrm{CH_3}$), 0.88 (3H, m; *s*-$\mathrm{CH_3}$), 1.24 (3H, d; J=7 Hz; $\mathrm{C\underline{H}_3\overset{|}{C}H-}$ in the side chain), 1.27 (3H, t; J=7 Hz; $\mathrm{C\underline{H}_3CH_2-}$), 3.04 (1H, q; J=7 Hz; $\mathrm{CH_3\overset{|}{C}\underline{H}CO_2C_2H_5}$), 3.71 (3H, s; $\mathrm{-CO_2CH_3}$) and 4.10 (2H, q; J=7 Hz; $\mathrm{-CO_2C\underline{H}_2CH_3}$); PMR ($\mathrm{C_6D_6}$) δ 0.78 (3H, s; *t*-$\mathrm{CH_3}$), 0.86 (3H, m; s-$\mathrm{CH_3}$), 1.03 (3H, t; J=7 Hz; $\mathrm{C\underline{H}_3CH_2-}$), 1.33 (3H, d; J=7 Hz; $\mathrm{C\underline{H}_3\overset{|}{C}H-}$ in the side chain), 3.29 (3H, s; $\mathrm{-CO_2CH_3}$), 3.32 (1H, q; J=7 Hz; $\mathrm{CH_3C\underline{H}\overset{|}{C}O_2C_2H_5}$), 4.02 (q, J=7 Hz; $\mathrm{-CO_2C\underline{H}_2CH_3}$) and 4.04 (q, J=7 Hz; $\mathrm{-CO_2C\underline{H}_2CH_3}$ of the other diastereomer); MS *m/e* 338 [$\mathrm{M^+(C_{19}H_{30}O_5)}$; 1%] and *m/e* 205 (100%). The substance (11 mg) was further chromatographed on a column of silica gel (5 g). Elution with a mixture of light petroleum and ether (5: 1) gave an analytical sample. Found: C, 67.63; H, 9.06%. Calcd for $\mathrm{C_{19}H_{30}O_5}$: C, 67.43; H, 8.94%. The product (**19**) corresponding to the least polar spot on tlc was a diastereomeric mixture as shown by the PMR spectral data mentioned above.

Fractions 17—23 gave the *O*-alkylated products (**20a** and **20b**; 69 mg in total; y: 26%), which corresponded to the other two spots. From fractions 20 and 21, more polar diastereomer (**20a**; 22 mg; one spot on tlc) was obtained as an oil, IR (liquid) 1755, 1730, 1700, and 1640 cm^{-1}; UV (EtOH) λ_{max} 247 nm(ε 12000); PMR ($CDCl_3$) δ 0.68 (3H, s; t-CH_3), 0.87 (3H, m; s-CH_3), 1.28 (3H, t; J=7 Hz; $C\underline{H}_3CH_2$–), 1.53 (3H, d; J=7 Hz; $C\underline{H}_3\overset{|}{C}H$– in the side chain), 3.72 (3H, s; –CO_2CH_3), 4.19 (2H, q; J=7 Hz; –$CO_2C\underline{H}_2CH_3$) and 4.59 (1H, q; J=7 Hz; $CH_3\overset{|}{C}\underline{H}CO_2C_2H_5$); PMR ($C_6D_6$) δ 0.63 (3H, s; t-CH_3), 0.77 (3H, m; s-CH_3), 0.97 (3H, t; J=7 Hz; $C\underline{H}_3CH_2$–), 1.47 (3H, d; J=7 Hz; $C\underline{H}_3\overset{|}{C}H$– in the side chain), 3.51 (3H, s; –CO_2CH_3), 3.94 (2H, q; J=7 Hz; –$CO_2C\underline{H}_2CH_3$) and 4.46 (1H, q; J=7 Hz; $CH_3\overset{|}{C}\underline{H}CO_2C_2H_5$); MS m/e 338 [$M^+(C_{19}H_{30}O_5)$; 3%] and m/e 205 (100%). The product (15 mg) was further chromatographed on a column of silica gel (3 g). Elution with a mixture of light petroleum and ether (4: 1) gave an analytical sample. Found: C, 67.17; H, 8.97%. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94%. From fractions 17 and 18, a small quantity of crude less polar diastereomer (**20b**) was obtained. Characterization of the latter diastereomer is described below.

(b) Alkylation of the keto-ester (**15**; 71 mg) in dry benzene (10 ml) with ethyl α-bromopropionate (385 mg) and sodium hydride (71 mg of a 50% dispersion in mineral oil) was carried out as described in (a) to give a residue (270 mg), which was chromatographed on a column of silica gel (20 g) using the following solvents as eluent: light petroleum and ether (20: 1) (frs 1—3, each 50 ml), light petroleum and ether (10: 1) (fr 4, 50 ml; frs 5—24, each 15 ml), and light petroleum and ether (5: 1) (frs 25—33, each 15 ml). Fractions 12—15 gave the C-alkylated product (**19**; 4 mg). The O-alkylated products (**20a** and **20b**; 40 mg in total) were obtained from fractions 16—33. Fractions 16—22 showing a single spot on tlc afforded less polar diastereomer (**20b**; 15 mg), an oil, IR (liquid) 1750—1730, 1715, and 1640 cm^{-1}; UV (EtOH) λ_{max} 245 nm (ε 4800); PMR ($CDCl_3$) δ 0.65 (3H, s; t-CH_3), 0.84 (3H, m; s-CH_3), 1.27 (3H, t; J=7 Hz; $C\underline{H}_3CH_2$–), 1.50 (3H, d; J=7 Hz; $C\underline{H}_3\overset{|}{C}H$– in the side chain), 3.69 (3H, s; –CO_2CH_3), 4.17 (2H, q; J=7 Hz; –$CO_2C\underline{H}_2CH_3$) and 4.55 (1H, q; J=7 Hz; $CH_3\overset{|}{C}\underline{H}CO_2C_2H_5$); PMR ($C_6D_6$) δ 0.64 (3H, s; t-CH_3), 0.77 (3H, m; s-CH_3), 0.94 (3H, t; J=7 Hz; $C\underline{H}_3CH_2$–), 1.53 (3H, d; J=7 Hz; $C\underline{H}_3\overset{|}{C}H$– in the side chain), 3.50 (3H, s; –CO_2CH_3), 3.93 (2H, q; J=7 Hz; –$CO_2C\underline{H}_2CH_3$) and 4.66 (1H, q; J=7 Hz; $CH_3\overset{|}{C}\underline{H}CO_2C_2H_5$); MS m/e 338 [$M^+(C_{19}H_{30}O_5)$; 2%] and m/e 205 (100%). The material (10 mg) was further chromatographed on a column of silica gel (3 g). Elution with a mixture of light petroleum and ether (10: 1) gave an analytical sample. Found: C, 67.09; H, 8.98%. Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94%. Fractions 25—33 gave more polar diastereomer (**20a**; 20 mg), whose spectral data were mentioned above.

*(±)-Tetrahydroligularenolide [(±)-**2**].* A mixture of the *C*-alkylated product (**19**; 65 mg), acetic acid (1 ml), water (0.3 ml), and 12 M hydrochloric acid (1.3 ml) was heated under reflux for 9 hr. Extraction with ether and the usual work-up gave an oil (49 mg), which was chromatographed on a column of silica gel (5 g). Elution with a mixture of light petroleum and ether (9: 1) and removal of the solvents afforded (±)-tetrahydroligularenolide [(±)-**2**; 24 mg; y: 57%], mp 83—84 °C, IR (CCl_4) 1770—1750 and 1690 cm^{-1}; UV (MeOH) λ_{max} 221 nm (ε 17000); PMR ($CDCl_3$) δ 0.58 (3H, s; t-CH_3), 0.91 (3H, d; J=6 Hz; s-CH_3), 1.80 (3H, t; J=1.5 Hz; CH_3-C=C), 2.77 (1H, d; J=14 Hz; proton at C-6β) and 4.58 (1H, m; proton at C-8); MS m/e 234 [$M^+(C_{15}H_{22}O_2)$; 21%] and m/e 123 (100%). Found: C, 76.79; H, 9.64%. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%. IR (in CCl_4), PMR and mass spectra of this substance were found to be identical with those of the authentic tetrahydroligularenolide [(−)-**2**]3) obtained from natural ligularenolide [(−)-**1**].3)

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