Total Synthesis of Racemic Ligularone and Isoligularone

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Racemic ligularone (2) and isoligularone (18) were synthesized from the *cis*-4aβ,5,6,7,8,8a-hexahydro-8β,8aβ-dimethylnapthalen-1,3(2*H*,4*H*)-dione (11) by furannulation reaction with diethylprop-2-ynylsulphonium bromide, prepared from diethyl sulfide and propargyl bromide.

Key words furanoeremophilanoid; ligularone; isoligularone; furannulation reaction; synthesis

The furanoeremophilanoids are present in plant terpenoids. A number of bicyclic and tricyclic eremophilane-furanoeremophilane sesquiterpenoids have been isolated and their structures determined. The fused 3-methylfuran structures and their biological activities have aroused interest and stimulated considerable synthetic efforts. In this paper we describe the total synthesis of racemic ligularone (**2**),[1—3] a representative furanoeremophilanoid isolated from *Ligularia sibirica* Coss., and its thermal isomerization product, isoligularone (**18**)[4,5] by furannulation reaction with the *cis*-4aβ,5,6,7,8,8a-hexahydro-8β,8aβ-dimethylnapthalen-1,3(2*H*,4*H*)-dione (**11**)[5] and diethylprop-2-ynylsulphonium bromide.[6,7] The latter is a reactive electrophile, which reacts with enolate anions of acyclic β-keto esters, β-keto sulfones, and β-diketones.

In previous papers, we have reported the synthesis of 2,4,5,6,7,7aβ-hexahydro-4β-hydroxy-3,6,6-trimethyl-1-benzofuran-2-one (**7**) as a model 6β-hydroxyeremophilenolide (**1**), as shown in Chart 1.[8] This reaction proceeded from dimedone (**4**) to compound **7** by *C*-alkylation, followed by lactonization. Firstly, we planned to study the synthetic route involving condensation of the bicyclic 1,3-diketone **11** with ethyl 2-iodopropionate (**5**) as well as a model route. Compound **11** was prepared starting from 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (**8**) and 2-methyl-2-cyclohexenone (**9**) in ten steps as reported by Miyashita *et al*. and shown in Chart 2.[5]

Although an attempt at alkylation of **11** with ethyl 2-iodopropionate (**5**) under basic conditions gave two *O*-alkylated compounds, *cis*-3-[1-(ethoxycarbonylethoxy)]-8β,9β-dimethyl-2-octalin-1-one (**12**) and *cis*-1-[1-(ethoxycarbonylethoxy)]-8β,9β-dimethyl-1-octalin-3-one (**13**), the desired *C*-alkylated bicyclic diketone **14** was not obtained, as shown in Table 1. Therefore, we changed the synthetic target from 6β-hydroxyeremophilenolide (**1**) to ligularone (**2**) using the key bicyclic 1,3-diketone **11**.

Firstly, we investigated the synthesis of 3,6,6-trimethyl-6,7-dihydrobenzofuran-4(5*H*)-one (**15**) as a model compound. The synthesis of compound **15** has involved the furannulation reaction of dimedone (**4**) with 1-nitro-1-(phenylthio)propene, KF or diethylprop-2-ynylsulphonium bromide as shown in Chart 3.[5,7] Initially, we studied the *C*-alkylation of **4** with acetol to give 3-hydroxy-2-[(1,2-dihydroxy-1-methyl)ethyl]-5,5-dimethyl-2-cyclohexen-1-one. Al-

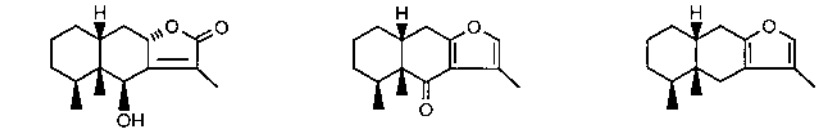

Fig. 1

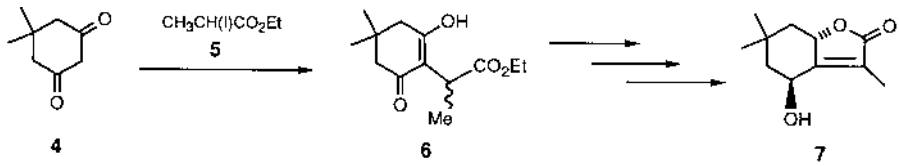

Chart 1

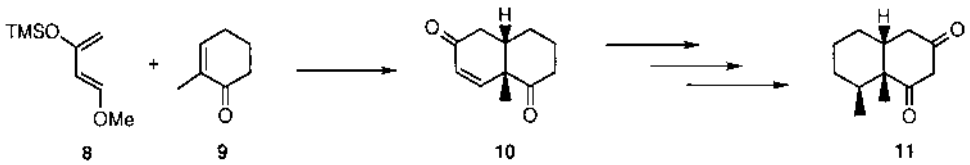

Chart 2

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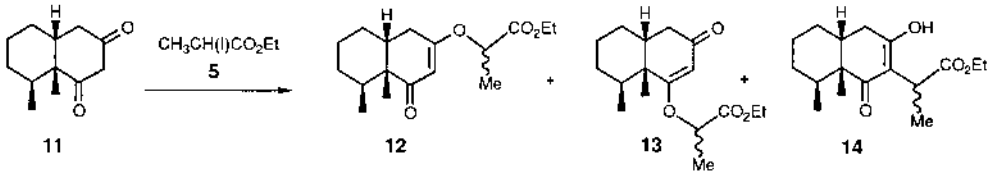
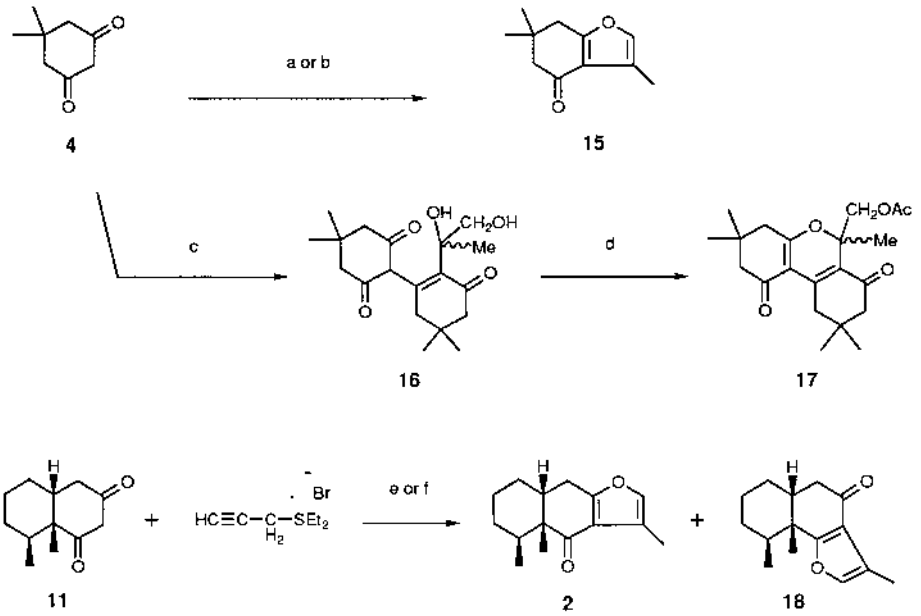
Table 1. Alkylation of Bicyclic 1,3-Diketone **11** with Ethyl 2-Iodopropionate (**5**)



Entry	Base	Solvent	Conditions	Yield (%)[a]		
				12	**13**	**14**
1	NaH	DMSO	r. t.,[b] 15 h	34	33	—
2	NaH	Benzene	r. t., 15 h	No reaction		
3	*n*-BuLi	THF	0 °C, 1 h—r. t., 15 h	24	21	—
4	K_2CO_3	Acetone	r. t., 15 h	30	32	—

a) Isolated yield. *b*) r. t.=Room temperature. —: Not isolated. DMSO: Dimethyl sulfoxide. THF: Tetrahydrofuran.



a) 1) $MeCH{=}C(SPh)NO_2$, KF, xylene. 2) $NaIO_4$, MeOH. 3) CCl_4 (Al_2O_3), △; b) $HC{\equiv}C\text{-}CH_2SEt_2^+\ Br^-$, NaOEt, EtOH; c) CH_3COCH_2OH, KF, PhH; d) Ac_2O, pyridine; e) NaOMe, MeOH; f) *tert*-BuOK, THF.

Chart 3

though the furannulation reaction of **4** with acetol under basic conditions was unsuccessful, treatment of **4** with acetol in the presence of KF in benzene afforded the dimeric condensation product, namely, **16**, $C_{19}H_{28}O_5$, mp 139—140.5 °C, (21.3% yield). The IR spectrum showed absorption bands at 3420 and 3250 cm^{-1} due to hydroxy groups, at 1734 and 1703 cm^{-1} due to ketonic groups, and at 1630 cm^{-1} due to an olefinic group. The ^{1}H-NMR spectrum showed the presence of five methyl groups at δ: 0.78 (3H, s), 1.09 (6H, s), 1.20 (3H, s), and 1.30 (3H, s), two hydroxy protons at δ: 1.45 (1H, s), and 1.77 (1H, s), ten methylenic protons at δ: 2.04—2.89 (8H, m), and 4.49 (2H, d, J=2.2 Hz), and a methinic proton at δ: 4.76 (1H, s). Thus, compound **16** was assigned as 2-[(1,2-dihydroxy-1-methyl)ethyl]-3-(4,4-dimethyl-2,6-dioxocyclohexyl)-5,5-dimethyl-2-cyclohexen-1-one, which is the dimeric condensation product. Acetylation of **16** with acetic anhydride in pyridine afforded the tricyclic 6*H*-dibenzo[*b*,*d*]pyrane product, namely, **17**, $C_{21}H_{28}O_5$, a colorless oil (82.3% yield). The IR spectrum showed an absorption band at 1765 and 1660 cm^{-1} due to ketonic groups and at 1635 cm^{-1} due to an olefinic group. The ^{1}H-NMR spectrum showed the presence of six methyl groups at δ: 1.06 (9H, s), 1.14 (3H, s), 1.52 (3H, s), and 2.13 (3H, s), and ten methylenic protons at δ: 2.18—2.47 (8H, m), and 4.39 (2H, d, J=0.7 Hz). Thus, compound **17** was assigned as 6-acetoxymethyl-1,2,3,4,7,8,9,10-octahydro-3,3,6,9,9-pentamethyl-6*H*-dibenzo[*b*,*d*]pyran-1,7-dione, which is the tricyclic product.

Next, we investigated the furannulation reaction using **11**. As the furannulation reaction of **11** with acetol was unsuccessful, we planned to study the formation of the fused 3-methylfuran by reaction of the enolate anion of **11** with the allenic sulfonium salt, diethylprop-2-ynylsulphonium bromide, which was obtained by reaction of diethyl sulfide and propargyl bromide. Reaction of **11** with diethylprop-2-ynylsulphonium bromide using NaOMe in MeOH or *tert*-BuOK

in tetrahydrofuran (THF) afforded two tricyclic furannulation products. In this, diethylprop-2-ynylsulphonium bromide was added to the THF solution of **11** and *tert*-BuOK. The mixture was reacted for 6 h at 10 °C to afford (±)-ligularone (**2**), $C_{15}H_{20}O_2$, mp 62—64 °C (lit.[3] mp 68—70 °C), (25.0% yield), and (±)-isoligularone (**18**), $C_{15}H_{20}O_2$, mp 110—113 °C (lit.[5] mp 111—114 °C), (41.7% yield). The racemic ligularone and isoligularone obtained were compared spectroscopically with data from authentic samples.

Experimental

All melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-200 spectrometer, and ^{1}H-NMR and ^{13}C-NMR spectra on a JEOL JNM-EX90 or JEOL JNM-α500 spectrometer, with tetramethylsilane as an internal standard. MS were recorded on a JEOL JMS-D 300 spectrometer. Elemental analyses were obtained using on a Yanaco CHN-corder MT-3. Wakogel C-200 (silica-gel) and Merck Kieselgel G nach Stahl (silica-gel) were used for column chromatography and thin-layer chromatography (TLC), respectively. All runs were carried out under argon.

***cis*-3-[1-(Ethoxycarbonylethoxy)]-8β,9β-dimethyl-2-octalin-1-one (12) and *cis*-1-[1-(Ethoxycarbonylethoxy)]-8β,9β-dimethyl-1-octalin-3-one (13)** A solution of *cis*-4aβ,5,6,7,8,8a-hexahydro-8β,8aβ-dimethylnapthalen-1,3(2*H*,4*H*)-dione (**11**)[5] (30 mg) in dry dimethyl sulfoxide (DMSO) (0.5 ml) was added to a mixture of NaH (7.4 mg) and dry DMSO (1.0 ml) and stirred at room temperature for 30 min. A solution of ethyl 2-iodopropionate (119 mg) in dry DMSO (0.5 ml) was then added and the mixture was stirred overnight at room temperature. The reaction mixture was poured into ice-water, and the aqueous layer was acidified with 10% HCl and extracted with chloroform. The organic layer was washed with water, then dried ($MgSO_4$) and concentrated. The residue was subjected to silica-gel chromatography (ethyl acetate : hexane, 1 : 1). The first eluate gave 25.5 mg (33.6%) **12** as a colorless oil. IR (neat) cm^{-1}: 1744, 1657, 1595. ^{1}H-NMR ($CDCl_3$) δ: 0.82 (1.5H, d, J=7.0 Hz, -Me), 0.83 (1.5H, d, J=7.0 Hz, -Me), 1.07 (3H, s, -Me), 1.28 (3H, t, J=7.0 Hz, -Me), 1.56 (3H, d, J=6.8 Hz, -Me), 1.60—2.67 (10H, m, methine H, methylene H), 4.22 (2H, q, J=7.3 Hz, methylene H), 4.62 (1H, q, J=6.8 Hz, methine H), 5.11 (1H, s, olefinic H). High-resolution EI-MS m/z: Calcd for $C_{17}H_{26}O_4$ (M^+): 294.1828. Found: 294.1811. The second eluate gave 25.0 mg (33.0%) **13** as a colorless oil. IR (neat) cm^{-1}: 1744, 1657, 1595. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (1.5H, d, J=8.6 Hz, -Me), 1.03 (1.5H, d, J=8.4 Hz, -Me), 1.20 (1.5H, s, -Me), 1.28 (1.5H, s, -Me), 1.27 (3H, t, J=6.6 Hz, -Me), 1.57 (3H, d, J=6.8 Hz, -Me), 1.60—2.72 (10H, m, methine H, methylene H), 4.17 (2H, q, J=7.3 Hz, methylene H), 4.60 (1H, q, J=6.6 Hz, methine H), 5.10 (1/2H, s, olefinic H), 5.12 (1/2H, s, olefinic H). High-resolution EI-MS m/z: Calcd for $C_{17}H_{26}O_4$ (M^+): 294.1828. Found: 294.1846.

2-[(1,2-Dihydroxy-1-methyl)ethyl]-3-(4,4-dimethyl-2,6-dioxocyclohexyl)-5,5-dimethyl-2-cyclohexen-1-one (16) A suspension of dimedone (**4**) (140 mg), acetol (148 mg) and KF (60 mg) in benzene was stirred overnight at room temperature. The aqueous layer was acidified with 10% HCl and extracted with chloroform. The organic layer was washed with water, then dried ($MgSO_4$) and concentrated. The residue was subjected to silica-gel chromatography (ethyl acetate : hexane, 1 : 3), and the eluate gave 71.5 mg (21.3%) **16** as colorless needles (ether–hexane), mp 139—140.5 °C. IR (KBr) cm^{-1}: 3420, 3250, 1734, 1703, 1630. ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, s, -Me), 1.09 (6H, s, -Me), 1.20 (3H, s, -Me), 1.30 (3H, s, -Me), 1.45 (1H, s, OH), 1.77 (1H, s, OH), 2.04—2.89 (8H, m, methylene H), 4.49 (2H, d, J=2.2 Hz, methylene H), 4.76 (1H, s, methine H). ^{13}C-NMR ($CDCl_3$) δ: 25.2, 25.6, 28.4, 28.8, 30.6, 30.9, 34.2, 37.8, 42.6, 51.3, 55.2, 55.5, 72.3, 82.8, 117.5, 176.4, 194.8, 202.0, 203.2. CI-MS m/z: 319 (M^+-H_2O+H). *Anal*. Calcd for $C_{19}H_{26}O_4$ ($M-H_2O$): C, 71.67; H, 8.23. Found: C, 71.79; H, 8.13.

6-Acetoxymethyl-1,2,3,4,7,8,9,10-octahydro-3,3,6,9,9-pentamethyl-6*H*-dibenzo[*b*,*d*]pyran-1,7-dione (17) Ac_2O (3.0 ml) was added to a solution of **16** (20 mg) in dry pyridine (1.0 ml) and the mixture was allowed to stand overnight at room temperature. The reaction mixture was poured into ice-water and then extracted with ethyl acetate. The ethyl acetate layer was washed with sat. $NaHCO_3$, dil. HCl, and H_2O, then dried ($MgSO_4$) and concentrated. The residue was subjected to silica-gel chromatography (ethyl acetate:hexane, 1 : 2), and the eluate gave 26.0 mg (82.3%) **17** as a colorless oil. IR (neat) cm^{-1}: 1765, 1660, 1635. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (9H, s, -Me), 1.14 (3H, s, -Me), 1.52 (3H, s, -Me), 2.13 (3H, s, -Me), 2.18—2.47 (8H, m, methylene H), 4.39 (2H, d, J=0.7 Hz, methylene H). ^{13}C-NMR ($CDCl_3$) δ: 21.6, 26.1, 27.7, 27.9, 28.4, 29.7, 32.3, 34.5, 38.2, 44.2, 46.0, 51.9, 52.4, 85.4, 119.4, 130.4, 161.6, 167.8, 174.6, 194.2, 199.5. High-resolution EI-MS m/z: Calcd for $C_{21}H_{28}O_5$ (M^+): 360.1935. Found: 360.1920.

(±)-Ligularone (2) and (±)-Isoligularone (18) To a solution of *tert*-BuOK (87 mg) in dry THF (2.5 ml) was added dropwise *cis*-4aβ,5,6,7,8,8a-hexahydro-8β,8aβ-dimethylnapthalen-1,3(2*H*,4*H*)-dione (**11**) (100 mg) dissolved in dry THF (2.5 ml). After stirring for 30 min at room temperature, the mixture was cooled to 10 °C and diethylprop-2-ynylsulphonium bromide (237 mg), which was prepared from diethyl sulfide and propargyl bromide, was added. The reaction mixture was stirred for 6 h at 10 °C and then poured into ice-water and extracted with ethyl acetate. The ethyl acetate layer was washed with 10% HCl, sat. $NaHCO_3$, then dried ($MgSO_4$) and concentrated. The residue was subjected to silica-gel chromatography (ethyl acetate : hexane, 1 : 19). The first eluate gave 29.9 mg (25.0%) **2** as colorless needles (ether–hexane), mp 62—64 °C (lit.[3] mp 68—70 °C). IR (KBr) cm^{-1}: 1665, 1640, 1570. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, d, J=7.0 Hz, -Me), 1.12 (3H, s, -Me), 1.33—1.66 (6H, m, methylene H), 2.20 (3H, d, J=1.2 Hz, -Me), 2.21—2.26 (2H, m, methine H), 2.75 (1H, d, J=13.4 Hz, methylene H), 2.91 (1H, d, J=15.6 Hz, methylene H), 7.06 (1H, t, J=0.6 Hz, olefinic H). High-resolution EI-MS m/z: Calcd for $C_{15}H_{20}O_2$ (M^+): 232.1463. Found: 232.1473. The second eluate gave 49.9 mg (41.7%) **18** as colorless needles (ether–hexane), mp 110—113 °C (lit.[5] mp 111—114 °C). IR (KBr) cm^{-1}: 1670, 1550. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, d, J=6.7 Hz, -Me), 1.31 (3H, s, -Me), 1.41—1.62 (5H, m, methylene H), 1.78—1.85 (1H, m, methylene H), 1.90—1.97 (1H, m, methine H), 2.20 (3H, d, J=1.4 Hz, -Me), 2.21—2.29 (2H, m, methine H, methylene H), 2.86 (2H, dd, J=16.7, 12.1 Hz, methylene H), 7.08 (1H, q, J=1.4 Hz, olefinic H). ^{13}C-NMR ($CDCl_3$) δ: 9.1, 16.6, 17.0, 20.4, 26.1, 29.9, 34.8, 39.7, 41.2, 42.1, 118.5, 119.0, 139.1, 174.5, 196.0. High-resolution EI-MS m/z: Calcd for $C_{15}H_{20}O_2$ (M^+): 232.1463. Found: 232.1473. Both synthetic products obtained were identified by comparison with data from authentic samples.[5]

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