Total Synthesis of Racemic Ligularone and Isoligularone

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Racemic ligularone (2) and isoligularone (18) were synthesized from the *cis*-4a β ,5,6,7,8,8a-hexahydro-8 β ,8a β -dimethylnaphthalen-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*-4a β ,5,6,7,8,8a-hexahydro-8 β ,8a β -dimethylnaphthalen-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 2,4,5,6,7,7a β -hexahydro-4 β -hydroxy-3,6,6-trimethyl-1-benzofuran-2-one (7) as a model 6 β -hydroxyeremophilanolide (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-(ethoxycarbonyloxy)]-8 β ,9 β -dimethyl-2-octalin-1-one (12) and *cis*-1-[1-(ethoxycarbonyloxy)]-8 β ,9 β -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 6 β -hydroxyeremophilanolide (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	<i>n</i> -BuLi	THF	0 °C, 1 h—r. t., 15 h	24	21	—
4	K ₂ CO 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)NO₂, KF, xylene. 2) NaIO₄, MeOH. 3) CCl₄ (Al₂O₃), Δ; b) HC≡C-CH₂SEt₂⁺ Br⁻, NaOEt, EtOH; c) CH₃COCH₂OH, KF, PhH; d) Ac₂O, 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**, C₁₉H₂₈O₅, 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 ¹H-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**, C₂₁H₂₈O₅, a color-

less 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 ¹H-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-ynylsulfonium bromide, which was obtained by reaction of diethyl sulfide and propargyl bromide. Reaction of **11** with diethylprop-2-ynylsulfonium 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 ($\pm$)-ligularone (**2**), C₁₅H₂₀O₂, mp 62–64 °C (lit.³) mp 68–70 °C), (25.0% yield), and ($\pm$)-isoligularone (**18**), C₁₅H₂₀O₂, 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 ¹H-NMR and ¹³C-NMR spectra on a JEOL JNM-EX90 or JEOL JNM- α 500 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)]-8 β ,9 β -dimethyl-2-octalin-1-one (12) and cis-1-[1-(Ethoxycarbonylethoxy)]-8 β ,9 β -dimethyl-1-octalin-3-one (13) A solution of *cis*-4 α ,5,6,7,8,8a-hexahydro-8 β ,8a β -dimethylnaphthalen-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 (MgSO₄) 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. ¹H-NMR (CDCl₃) 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 C₁₇H₂₆O₄ (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. ¹H-NMR (CDCl₃) 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 C₁₇H₂₆O₄ (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 (MgSO₄) 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. ¹H-NMR (CDCl₃) 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). ¹³C-NMR (CDCl₃) 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⁺–H₂O+H). Anal. Calcd for C₁₉H₂₆O₄ (M–H₂O): 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-pentamethyl-6*H*-dibenzo[*b,d*]pyran-1,7-dione (17) Ac₂O (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. NaHCO₃, dil. HCl, and H₂O, then dried (MgSO₄) 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. ¹H-NMR (CDCl₃) 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). ¹³C-NMR (CDCl₃) 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 C₂₁H₂₈O₅ (M⁺): 360.1935. Found: 360.1920.

($\pm$)-Ligularone (2) and ($\pm$)-Isoligularone (18) To a solution of *tert*-BuOK (87 mg) in dry THF (2.5 ml) was added dropwise *cis*-4 α ,5,6,7,8,8a-hexahydro-8 β ,8a β -dimethylnaphthalen-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. NaHCO₃, then dried (MgSO₄) 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. ¹H-NMR (CDCl₃) 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 C₁₅H₂₀O₂ (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. ¹H-NMR (CDCl₃) 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). ¹³C-NMR (CDCl₃) 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 C₁₅H₂₀O₂ (M⁺): 232.1463. Found: 232.1473. Both synthetic products obtained were identified by comparison with data from authentic samples.⁵⁾

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