3β-Angeloyloxy-10β-hydroxy-9β-senecioyloxyfuranoeremophilane and 3β-Angeloyloxy-10β-hydroxyfuranoeremophilane. New Furanoeremophilane Derivatives from *Farfugium japonicum* Kitamura[1)]

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(Received April 22, 1978)

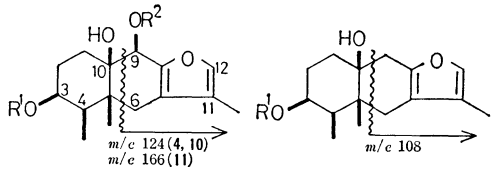
Two new furanoeremophilane derivatives isolated from *Farfugium japonicum* Kitamura have been shown to be 3β-angeloyloxy-10β-hydroxy-9β-senecioyloxyfuranoeremophilane and 3β-angeloyloxy-10β-hydroxyfuranoeremophilane.

In the previous papers[2,3)] we have reported the isolation and structure determination of furanosesquiterpenes from *Farfugium japonicum* Kitamura (= *Ligularia tussilaginea* Makino). Two additional furanoeremophilane derivatives have now been isolated from the same plant. In this paper we wish to present evidence leading to 3β-angeloyloxy-10β-hydroxy-9β-senecioyloxyfuranoeremophilane (**1**) and 3β-angeloyloxy-10β-hydroxyfuranoeremophilane (**2**) for these new sesquiterpenes.

Compound **1**, a viscous oil, was positive to the Ehrlich test. The IR, UV, PMR, and mass spectra (*cf.* Experimental and Table 1) suggest the presence of a β-methyl-substituted furan ring with an α-proton, a tertiary hydroxyl, an angeloyloxyl, and a senecioyloxyl group.[3)] The PMR spectrum also shows the presence of a secondary and a tertiary methyl group. This sesquiterpene (**1**) was converted in five steps into the known acetoxy ketone (**3**) as follows.

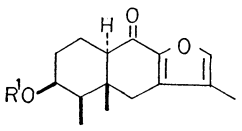
Reduction of **1** with lithium aluminium hydride gave a triol (**4**), which was oxidized with active manganese dioxide[4)] in benzene to yield a dihydroxy ketone (**5**). Acetylation of **5** with acetic anhydride in pyridine at room temperature gave a monoacetate (**6**), whose IR spectrum still shows an absorption due to a tertiary hydroxyl group. The tertiary hydroxyl group of **6** was replaced by bromine atom using phosphorus tribromide in dichloromethane[5)] to give an α-bromo ketone (**7**). Debromination of **7** with active zinc dust in acetic acid[6)] afforded an acetoxy ketone (**3**), which was found to be identical (mp, mmp, $[\alpha]_D$, IR, PMR, and mass spectra) including absolute configuration with 3β-acetoxy-9-oxo-10α*H*-furanoeremophilane (**3**) prepared from epieuryopsonol[3,7)] (**8**; 3β-hydroxy-9-oxo-10α*H*-furanoeremophilane). Thus a 9-oxygenated furanoeremophilane skeleton with 3β-hydroxyl or 3β-acyloxyl group was shown for this series of compounds (**1**, **3**—**7**). The absolute configuration at C-3 was further confirmed as *S* by applying the Horeau's method[8)] to **5** (esterification 36%; optical yield (−) 62%).

The 9-oxo structure for both the dihydroxy ketone (**5**) and the monoacetate (**6**) received support from their UV spectra (λ_{max} 283—285 nm, ε 8800—9300).[3,9)] The tertiary hydroxyl group of **6** could only be placed on either C-10 or C-4. As the PMR spectrum of **6** shows the presence of a secondary methyl group (at C-4), this tertiary hydroxyl group must be located on C-10. Therefore, the triol (**4**) should be 3β, 6ξ, 10ξ-trihydroxyfuranoeremophilane. To confirm this result, the triol (**4**) was treated with chromium trioxide in pyridine to give 10ξ-hydroxy-3,9-dioxofuranoeremophilane (**9**); in the PMR spectrum of **9** a doublet due to a secondary methyl group (at C-4) was observed.



	R¹	R²
1	-CO-C(CH₃)=CH-CH₃	-CO-CH=C(CH₃)-CH₃
4	H	H
10	-CO-C(CH₃)=CH-CH₃	H
11	-COCH₃	-COCH₃

	R¹
2	-CO-C(CH₃)=CH-CH₃
14	H
16	-COCH₃



	R¹
3	-COCH₃
8	H

Treatment of **1** with ethanolic potassium hydroxide at room temperature gave a partially hydrolyzed compound (**10**). Spectral data of **10** show the presence of a secondary hydroxyl group and the absence of a senecioyloxyl group. Compound **10** is thus a decenecioyl derivative of **1**. In the PMR spectrum of **10** an allylic proton on hydroxyl-bearing carbon atom resonates at δ (C_6D_6) 4.31, while the corresponding allylic proton signal of **1** at δ (C_6D_6) 6.05. This observation shows that the hydroxyl group of **10** and the senecioyloxyl group of **1** are located on C-9. Therefore, **1** must be 3β-angeloyloxy-10ξ-hydroxy-9ξ-senecioyloxyfuranoeremophilane. The configurations at C-9 and at C-10 were determined as follows.

Acetylation of **4** with acetic anhydride in pyridine gave a diacetate (**11**). In the PMR sepctrum of **11** at 25 °C, two broad signals due to $C_{(9)}$–H and $C_{(12)}$–H appear at δ (CS_2) 5.48 and 6.97, respectively. At −40 °C these signals changed into a pair of signals at δ (CS_2) 5.26 (half-band width: $W_{1/2}$=3 Hz) and 6.02 ($W_{1/2}$=5 Hz) and δ (CS_2) 6.96 and 6.86 in a ratio of *ca.* 5:1, respectively; this indicates that **11** has

TABLE 1. PMR SPECTRAL DATA (δ values)[a]

	1		2	
	CCl_4	C_6D_6	CCl_4	C_6D_6
$C_{(4)}$-CH_3	1.06m		1.05 d J=6	1.08 d J=6
$C_{(5)}$-CH_3	1.18 s	1.31 s	1.08 s	1.03 s
$C_{(11)}$-CH_3	1.90	1.65 d J=1	1.90	1.75 d J=1.5
$C_{(3)}$-H	5.20m	5.22m	5.20m	5.20m
$C_{(9)}$-H	5.70m	6.05m		
$C_{(12)}$-H	7.04m	6.92m	6.93m	6.99m
CH_3(H)C=C(CO-CH_3)	1.90	1.90	1.90m	1.82m
CH_3(H)C=C(CO-CH_3)	1.98	1.99 d J=8	1.99 d J=7	2.02 d J=7
CH_3(CH_3)C=C(CO-H)	2.18	2.07m	—	—
CH_3(CH_3)C=C(CO-H)	1.90	1.31 d J=1.5	—	—
CH_3(H)C=C(CO-CH_3)	5.95	5.72 q J=8	5.98 q J=7	5.75 q J=7
CH_3(CH_3)C=C(CO-H)	5.65m	5.55m	—	—

a) Coupling constants are expressed in Hz. s: singlet, d: doublet, q: quartet, m: multiplet.

a *cis*-AB-ring junction and exists in two interchangeable conformational isomers, so-called "steroid-like" (**11-A**) and "non-steroid-like" (**11-B**) chair-chair conformer.[10] A broad signal ($W_{1/2}$=*ca.* 22 Hz; axial proton) at δ (CS_2) 4.92 assigned to the 3α-proton in **11** suggests that **11** has predominantly the "non-steroid-like" conformation (**11-B**) at −40 °C.

Reduction of **5** with lithium aluminium hydride gave **4** and its C-9 epimer (**12**) in a ratio of 1:1. Acetylation of **12** with acetic anhydride in pyridine afforded a diacetate (**13**). In the PMR spectrum of **13** at 25 °C a broad signal of the C-12 proton was observed at δ (CS_2) 6.93. When the temperature was lowered to −40 °C this signal changed into a pair of signals at δ (CS_2) 6.89 and 6.97 in a ratio of 5:1. The broad signal ($W_{1/2}$=*ca.* 22 Hz) at δ (CS_2) 5.03 due to the C-3 proton indicates that the "non-steroid-like" conformer is the major one. The half-band width (5 Hz) observed for the PMR signal δ (CS_2) 5.52 of C-9 proton in **13** is larger than that (3 Hz) for the signal δ (CS_2) 5.26 of C-9 proton in **11**. This implies that the C-9 proton in **13** has a quasi-axial nature ("non-steroid-like" conformation) and that the C-9 proton in **11** has a quasi-equatorial nature ("non-steroid-like" conformation).[11] Therefore, the acetoxyl group at C-9 of **11** and **13** are in β- and α-configuration, respectively. The structure including absolute configuration of **1** is represented by 3β-angeloyloxy-10β-hydroxy-9β-senecioyloxyfuranoeremophilane.

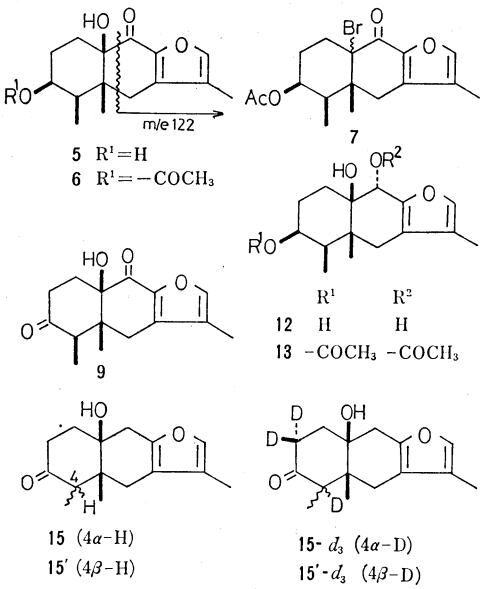
Compound **2** was also positive to the Ehrlich test. From the UV, IR, PMR, and mass spectra **2** is assumed to be the desenecioyloxyl derivative of **1** (*cf.* Experimental and Table 1).

Reduction of **2** with lithium aluminium hydride in ether gave a diol (**14**), which was also obtained by alkaline hydrolysis of **2**.

Oxidation of **14** with chromium trioxide in pyridine gave a hydroxy ketone (**15**). Deuterium-exchange reaction of **15** with CH_3OD in the presence of a trace of alkali afforded a mixture of deuterated products (**15**-d_3 and **15'**-d_3), whose mass spectrum shows an incorporation of three deuterium atoms. A doublet at δ 0.94 due to the secondary methyl in **15** changed into a pair of singlets at δ 0.94 (**15**-d_3) and δ 1.01 (**15'**-d_3). The carbonyl group of **15** and hence the secondary hydroxyl group of **14** could be placed on C-3, provided that these compounds have a furanoeremophilane skeleton.

Carbon skeleton including absolute configuration of the above compounds was determined on the basis of the following transformation. Reduction of **11** with lithium in ethylamine[12] yielded 3β,10β-dihydroxyfuranoeremophilane. Its spectroscopic data (IR, PMR, and mass spectra) are in complete accord with those of **14**. The absolute configuration (*S*) at C-3 in **14** was further confirmed by the Horeau's method[8] (esterification 100%; optical yield (−) 28%). Compounds **2**, **14**, and **15** were thus shown to be 3β-angeloyloxy-10β-hydroxyfuranoeremophilane, 3β,10β-dihydroxyfuranoeremophilane, and 10β-hydroxy-3-oxofuranoeremophilane, respectively.

In further support for the proposed structures, the intense peak at *m/e* 108 due to the *retro*-Diels-Alder fragmentation in ring B[13] was observed for the furanoeremophilane derivatives (**2**, **14**, and **16**), and the corresponding peaks at *m/e* 124, *m/e* 166, and *m/e* 122 for the compounds with 9-hydroxyl (**4** and **10**), 9-acetoxyl (**11** and **13**), and 9-oxo (**3**, **5**, **6**, and **9**) group, respectively.



In the PMR spectra (Table 2) of the hydroxy ketone (**15**), a remarkable pyridine-induced solvent shift[14] ($\delta^{CDCl_3}-\delta^{C_5H_5N}=-0.17$) of the tertiary methyl at C-5 arising from preferential association of pyridine with the hydroxyl group was observed. The carbonyl group at C-3 would cause[15] a small and positive solvent shift of the tertiary methyl signal for both structures

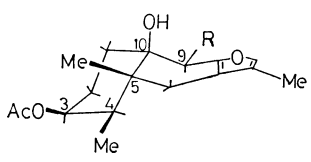
Table 2. Chemical shifts (δ values) and solvent shifts (Δ values) of methyl protons for compounds **15** and **15′-d_3**

Compound	Solvent	$C_{(4)}$-CH_3	$C_{(5)}$-CH_3	$C_{(11)}$-CH_3
15	CCl_4	0.94	0.92	1.87
	C_6H_6	0.94	0.76	1.73
	$\Delta^{CCl_4}_{C_6H_6}$	0.00	+0.16	+0.14
	$CDCl_3$	1.02	0.99	1.95
	C_5H_5N	1.10	1.16	1.92
	$\Delta^{CDCl_3}_{C_5H_5N}$	−0.08	−0.17	+0.03
15′-d_3	CCl_4	1.01	1.04	1.84
	C_6H_6	1.05	0.84	1.63
	$\Delta^{CCl_4}_{C_6H_6}$	−0.04	+0.21	+0.21

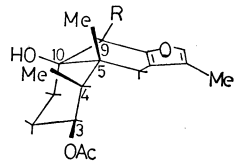
$\Delta^{CDCl_3}_{C_5H_5N}=\delta^{CDCl_3}-\delta^{C_5H_5N}$, $\Delta^{CCl_4}_{C_6H_6}=\delta^{CCl_4}-\delta^{C_6H_6}$.

with *cis*- and *trans*-AB-ring junction. The extent of the negative solvent shift value for the tertiary methyl suggests the structure with a *cis*-AB-ring junction for **15**, in which the dihedral angle between the hydroxyl group and the tertiary methyl would be approximately 60°, while a small solvent shift ($\delta^{CDCl_3}-\delta^{C_5H_5N}$ = *ca.* −0.04) is expected for the structure with a *trans*-AB-ring junction. This shows that the solvent shift is applicable for the structure determination of these compounds.

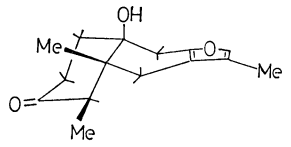
A small benzene-induced solvent shift[16] (Table 2) for the C-4 methyl signal adjacent to carbonyl group was observed in the PMR spectra of **15** and **15′-d_3**; this suggests equatorial nature for the secondary methyl. **15** and **15′-d_3** must exist preferably in a "steroid-like" (**15-A**) and in a "non-steroid-like" (**15′-d_3-B**) conformation, respectively.



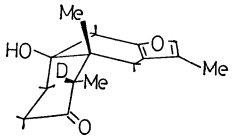
11-A (R=OAc)
16-A (R=H)



11-B (R=OAc)
16-B (R=H)



15-A



15′-B

Acetylation of **14** with acetic anhydride in pyridine gave a monoacetate (**16**). The PMR spectrum in carbon disulfide at 30 °C showed a signal at δ 5.06 (quintet, J=*ca.* 4 Hz) due to the proton at C-3. As the temperature was lowered the signal broadened and at −46 °C the signal changed into a pair of signals at δ 4.78 (s, $W_{1/2}$ *ca.* 8 Hz) and δ 5.07 (quintet, J=*ca.* 5.5 Hz) in a ratio of 1:3, which are assigned to the C-3α proton (equatorial) in the "steroid-like" conformation (**16-A**) and the C-3α proton (axial) in the "non-steroid-like" conformation (**16-B**), respectively. An equilibrium between the "steroid-like" (**A**) and "non-steroid-like" (**B**) conformations on PMR time scale at room temperature was thus shown for **16**.

Experimental

IR, UV, and mass spectra were measured using a Hitachi EPI-G2, a Hitachi EPS-3, and a Hitachi RMU-6-Tokugata, spectrometers, respectively. Optical rotations, $[\alpha]_D$, were measured with a JASCO DIP-SL spectrometer. PMR spectra were taken on a JEOL PS-100 (100 MHz), a Hitachi R-20 (60 MHz), or a Hitachi R-24 (60 MHz) spectrometer. Chemical shifts are expressed in δ (TMS as an internal standard), and coupling constants in Hz. All melting points were determined on a hot block and reported uncorrected. Merck Kieselgel G and Kieselgel 60 PF_{254} were used for analytical and preparative TLC, respectively. For column chromatography, silica gel (Wakogel C-200) was used.

Isolation of 3β-Angeloyloxy-10β-hydroxy-9β-senecioyloxyfuranoeremophilane (1) and 3β-Angeloyloxy-10β-hydroxyfuranoeremophilane (2). The roots of *Farfugium japonicum* Kitamura (15 kg) were extracted with ether at room temperature for 3 days. The extract was then filtered, dried over anhydrous sodium sulfate, and the solvent was evaporated to give a viscous oil (80 g). The oil (36 g) was chromatographed on silica gel (500 g) using light petroleum–ether (10:1) as eluent. The eluted fractions (each 400 ml) were collected and examined by TLC. Fractions 10 and 11 gave a viscous oil (959 mg), containing **1**, which was purified by preparative TLC. Fractions 15—17 gave a viscous oil (1.06 g). The oil was purified by preparative TLC to afford **2**.

3β-Angeloyloxy-10β-hydroxy-9β-senecioyloxyfuranoeremophilane (1). Compound **1** (one spot on TLC), an oil, $[\alpha]_D^{16}$ +79° (*c* 1.05, EtOH), was positive to the Ehrlich test (pink in color). Characterization of **1** is as follows; UV (MeOH): λ_{max} 220 nm (ε 37000); IR(neat): 3500, 1710, and 1642 cm^{-1}; PMR (Table 1); MS: *m/e* 430 [1%, M^+ ($C_{25}H_{34}O_6$)], 412 (3%, $[M-H_2O]^+$), 83 (100%, $[CH_3CH=C(CH_3)CO]^+$ and $[(CH_3)_2C=CHCO]^+$) and 55 (42%, $[CH_3CH=CCH_3]^+$ and $[(CH_3)_2C=CH]^+$).

3β-Angeloyloxy-10β-hydroxyfuranoeremophilane (2). Compound **2** (one spot on TLC) was a viscous oil, $[\alpha]_D^{24}$ −13° (*c* 0.88, EtOH). Its spot on TLC plate showed purple color to the Ehrlich test. Spectral data of **2** are as follows; UV (MeOH): λ_{max} 218.5 nm (ε 19000); IR (CCl_4): 3500, 1710, 1645, and 1565 cm^{-1}; PMR (Table 1); MS: *m/e* 332 [6%, M^+ ($C_{20}H_{28}O_4$)], 124 (41%), 109 (100%), 108 (75%, *retro*-Diels-Alder fragment[13]), 83 (89%, $[CH_3CH=C(CH_3)CO]^+$), and 55 (64%, $[CH_3CH=CCH_3]^+$).

Reduction of 1 with Lithium Aluminium Hydride. To a suspension of lithium aluminium hydride (100 mg) in dry ether (6 ml) a solution of **1** (125 mg) in dry ether (6 ml) was added and the mixture was refluxed for 2.5 h under a nitrogen atmosphere. An excess of lithium aluminium hydride was decomposed with water and the product was extracted with ether. The usual treatment of the extract gave a crystalline product (86 mg), which was purified by preparative TLC (developed with ether) to afford 3β,9β,10β-trihydroxyfuranoeremophilane (**4**: 34 mg), mp 158—159 °C (dec), $[\alpha]_D^{25}$ −5° (*c* 1.0, MeOH); UV (MeOH): λ_{max} 224 nm (ε 4200); IR (Nujol): 3250—3460 cm^{-1}; PMR ($CDCl_3$): δ 1.10 (d, J=6.5 Hz, $C_{(4)}$-CH_3), 1.21 (s, $C_{(5)}$-CH_3), 1.90 (d, J=1.2 Hz, $C_{(11)}$-CH_3), 2.15 (d, J=17 Hz, $C_{(6)}$-H),

2.53 (d, J=17 Hz, $C_{(6)}$-H), 4.02 (m, $C_{(3)}$-H), 4.47 (br s, $C_{(9)}$-H), and 7.12 (q, J=1.2 Hz, $C_{(12)}$-H); MS: *m/e* 124 (100%, *retro*-Diels-Alder fragment). A molecular ion peak at *m/e* 266 ($C_{15}H_{22}O_4$) was not observed. Found: C, 67.74; H, 8.17%. Calcd for $C_{15}H_{22}O_4$: C, 67.84; H, 8.33%.

Oxidation of ***4*** *with Active Manganese Dioxide.* To a solution of **4** (40 mg) in benzene (30 ml) was added active manganese dioxide (70 mg) and the mixture was stirred for 8 h under a nitrogen atmosphere. After filtration, the solvent was removed to give 3β,10β-dihydroxy-9-oxofuranoeremophilane (**5**; 26 mg); negative to the Ehrlich test; mp 138 °C (recrystallized from light petroleum–ether), $[\alpha]_D^{25}$ −18° (c 0.59, MeOH); UV (MeOH): λ_{max} 283 nm (ε 8800); IR (Nujol): 3450, 3340, 1670, 1605, and 1530 cm^{-1}; MS: *m/e* 264 [20%, M^+ ($C_{15}H_{20}O_4$)] and 122 (100%, *retro*-Diels-Alder fragment). Found: C, 68.43; H, 7.56%. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63%.

Acetylation of ***5*** *with Acetic Anhydride in Pyridine.* Compound **5** (140 mg) was treated with acetic anhydride (1.5 ml) and pyridine (3 ml) overnight at room temperature. Methanol (2 ml) was added to decompose an excess of acetic anhydride. Evaporation of the solvent gave an oily residue which was chromatographed on silica gel (7 g) using hexane–ether (2:1; 75 ml) as eluent to yield the monoacetate, 3β-acetoxy-10β-hydroxy-9-oxofuranoeremophilane (**6**; 157 mg; one spot on TLC), an amorphous solid, IR (Nujol): 3450, 1735, and 1675 cm^{-1}; PMR (CCl_4): δ 0.98 (s, $C_{(5)}$-CH_3), 1.08 (d, J=*ca.* 7 Hz, $C_{(4)}$-CH_3), 2.00 (s, $C_{(11)}$-CH_3 and -OCOCH_3), 5.20 (m, $C_{(3)}$-H), and 7.37 (br s, $C_{(12)}$-H); MS: *m/e* 306 [6%, M^+ ($C_{17}H_{22}O_5$)], 263 (5%, [M−CH_3-CO]$^+$), 246 (11%, [M−CH_3COOH]$^+$), 124 (66%), 123 (63%), and 122 (100%, *retro*-Diels-Alder fragment).

Treatment of ***6*** *with Phosphorus Tribromide.* To a solution of **6** (73 mg) in dichloromethane (9 ml) was added a solution of phosphorus tribromide (0.1 ml) in dichloromethane (0.9 ml) and the reaction mixture was heated under reflux for 4 h under a nitrogen atmosphere. The reaction mixture was then cooled to 0 °C and a saturated aqueous solution of sodium hydrogencarbonate (5 ml) was added dropwise. The product was extracted three times with ether and a combined ethereal solution was washed with water and with saturated brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oily product, 3β-acetoxy-10 ξ-bromo-9-oxofuranoeremophilane (**7**; 56 mg; one spot on TLC), IR (neat): 1730 and 1670 cm^{-1}; PMR (CCl_4): δ 1.00 (d, J=*ca.* 7 Hz, $C_{(4)}$-CH_3), 1.11 (s, $C_{(5)}$-CH_3), 1.99 (s, $C_{(11)}$-CH_3 and -OCOCH_3), 4.98 (m, $C_{(3)}$-H, $W_{1/2}$=*ca.* 12 Hz), and 7.34 (m, $C_{(12)}$-H); MS: *m/e* 370 [13%, M^+ ($C_{17}H_{21}O_4Br$)], 368 (13%, M^+), 289 (24%, [M−Br]$^+$), and 229 (100%, [M−Br−CH_3-COOH]$^+$).

Debromination of ***7*** *with Active Zinc Dust in Acetic Acid.* To a solution of **7** (56 mg) in acetic acid (3 ml) was added active zinc dust (107 mg) and the mixture was allowed to stir for 3.5 h at room temperature under a nitrogen atmosphere. Ether was then added. After filtration the solvent was evaporated under reduced pressure to give an oily residue, which was chromatographed on silica gel (7 g). Elution with hexane–ether (2:1, 100 ml) and hexane–ether (1:1, 80 ml) gave colorless crystals (30 mg). Recrystallization from hexane–ether afforded 3β-acetoxy-9-oxo-10α*H*-furanoeremophilane (**3**; 17 mg) as colorless needles, mp 172—174 °C, $[\alpha]_D^{28}$ +27° (c 0.55, MeOH), IR (Nujol): 1720 and 1655 cm^{-1}; PMR ($CDCl_3$): δ 0.98 (s, $C_{(5)}$-CH_3), 1.04 (d, J=*ca.* 7 Hz, $C_{(4)}$-CH_3), 2.00 (d, J=*ca.* 1 Hz, $C_{(11)}$-CH_3), 2.06 (s, -OCOCH_3), 5.01 (m, $C_{(3)}$-H), and 7.37 (m, $C_{(12)}$-H); *m/e* 290 [35%, M^+($C_{17}H_{22}O_4$)], 230 (58%, [M−CH_3COOH]$^+$), 215 (51%, [M−CH_3COOH−CH_3]$^+$), 162 (100%), and 122 (77%, *retro*-Diels-Alder fragment). This compound was found to be identical (mp, mixed mp, IR, PMR, and mass spectra) with **3** prepared from **8** (*vide infra*).

Acetylation of ***8*** *with Acetic Anhydride in Pyridine.* A solution of epieuryopsonol (**8**; 22 mg) in acetic anhydride (2 ml) and pyridine (3 ml) was allowed to stand overnight at room temperature to yield **3**, colorless needles (recrystallization from hexane–ether), mp 173—175 °C, $[\alpha]_D^{28}$ +28° (c 0.53, MeOH), IR (Nujol): 1720 and 1655 cm^{-1}; PMR ($CDCl_3$): δ 0.98 (s, $C_{(5)}$-CH_3), 1.04 (d, J=*ca.* 7 Hz, $C_{(4)}$-CH_3), 2.00 (d, J=*ca.* 1 Hz, $C_{(11)}$-CH_3), 2.06 (s, -OCOCH_3), 5.03 (m, $C_{(3)}$-H)l and 7.36 (m, $C_{(12)}$-H); MS: *m/e* 290 [32%, M^+($C_{17}H_{22}O_4$)], 230 (54%, [M−CH_3COOH]$^+$), 215 (48%, [M−CH_3COOH−CH_3]$^+$), 162 (100%), and 122 (77%. *retro*-Diels-Alder fragment). Found: C, 70.33; H, 7.90%. Calcd for $C_{17}H_{22}O_4$: C, 70.34; H, 7.64%.

Application of the Horeau's Method to ***5****.* A solution of **5** (20.6 mg, 0.078 mmol) in pyridine (0.3 ml) was allowed to stand with α-phenylbutyric anhydride (85.0 mg, 0.259 mmol) overnight. The reaction mixture was then heated with one drop of water. After benzene was added, the mixture was titrated with 0.1 M potassium hydroxide solution in the presence of phenolphthalein. The aqueous layer was acidified with dilute sulfuric acid and then extracted with benzene. After usual treatment of the extract, the solvent was distilled off to give α-phenylbutyric acid. The optical rotation value (α_D −0.027°) was observed for benzene solution (1.5 ml) of the acid using a 0.1 dm cell. Esterification 36%; optical yield (−) 62%.

Oxidation of ***4*** *with Chromium Trioxide in Pyridine.* To a solution of chromium trioxide (419 mg) in pyridine (6 ml) was added a solution of **4** (193 mg) in pyridine (3 ml) with stirring at 0 °C. The mixture was allowed to stand for 24 h at room temperature under a nitrogen atmosphere, diluted with a mixture of ice and water, and extracted with ether. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed to give a residue (77 mg) which was chromatographed on silica gel (5 g; eluent: light petroleum–ether, 1:1) to give 10β-hydroxy-3,9-dioxofuranoeremophilane (**9**; 25 mg), mp 121—122 °C (recrystallization from light petroleum–ether); UV (EtOH): λ_{max} 285 nm (ε 9300); IR (Nujol): 3430, 1700, 1655, and 1530 cm^{-1}; PMR ($CDCl_3$): δ 1.05 (s, $C_{(5)}$-CH_3), 1.33 (d, J=7.5 Hz, $C_{(4)}$-CH_3), 1.97 (d, J=1 Hz, $C_{(11)}$-CH_3), 3.73 (s, OH; this signal disappeared on addition of D_2O), and 7.48 (q, J=1 Hz, $C_{(12)}$-H); MS: *m/e* 262 [34%, M^+($C_{15}H_{18}O_4$)], 178 (41%), and 122 (100%, *retro*-Diels-Alder fragment). Found: C, 68.57; H, 6.85%. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92%.

Partial Hydrolysis of ***1*** *with Ethanolic Potassium Hydroxide.* A solution of potassium hydroxide (50 mg) in 95% ethanol (1 ml) was added to **1** (33 mg), and the solution was allowed to stand at room temperature for 3 h. To the reaction mixture was added water (10 ml), and the resulting aqueous solution was extracted with ether (each 30 ml) three times. A combined ethereal solution was washed with 10% hydrochloric acid (10 ml), saturated aqueous solution of sodium hydrogencarbonate (10 ml), and with water (20 ml), and finally dried over anhydrous sodium sulfate. Evaporation of the solvent gave a residue (23 mg), which was passed through a column of silica gel (200 mg) (eluent: light petroleum–ether, 2:1) to give partially hydrolyzed product (**10**; one spot on TLC), a viscous oil; IR (neat): 3450, 1710, 1640, and 1560 cm^{-1}; PMR (C_6D_6): δ 1.10 (m, $C_{(4)}$-CH_3), 1.17 (s, $C_{(5)}$-CH_3), 1.73 (d, J=*ca.* 1 Hz, $C_{(11)}$-CH_3), 1.95

(m, $-COC(CH_3)=CHCH_3$), 2.05 (d, $J=7$ Hz, $-COC(CH_3)=CHCH_3$), 4.31 (br s, $C_{(9)}$–H), 5.30 (m, $C_{(3)}$–H), 5.80 (q, $J=7$ Hz, $-CO(CH_3)C=CHCH_3$), and 7.05 (m, $C_{(12)}$–H); MS: *m/e* 348 [0.8%, M^+ ($C_{20}H_{28}O_5$)]. 330 (0.6%, [M−H_2O]$^+$), 124 (100%, *retro*-Diels-Alder fragment), 83 (20%, [$COC(CH_3)=CHCH_3$]$^+$), and 55 (21 %, [$C(CH_3)=CHCH_3$]$^+$).

Acetylation of ***4*** *with Acetic Anhydride in Pyridine.* A mixture of **4** (51 mg), acetic anhydride (0.2 ml), and pyridine (0.5 ml) was allowed to stand overnight at room temperature. After addition of methanol (1 ml), the solvent was removed under reduced pressure to give a residue. From the residue 3*β*, 9*β*-diacetoxy-10*β*-hydroxyfuranoeremophilane (**11**; one spot on TLC), an oil, was isolated by preparative TLC (developed with light petroleum–ether, 1:1). Spectral data of **11** are as follows ; IR (neat): 3480, 1735, and 1560 cm^{-1}; PMR (CCl_4): δ 1.05 (d, $J=7$ Hz, $C_{(4)}$–CH_3), 1.13 (s, $C_{(5)}$–CH_3), 1.92 (d, $J=ca.$ 1 Hz, $C_{(11)}$–CH_3), 2.00 (s, $-OCOCH_3$), 2.10 (s, $-OCOCH_3$), 5.10 (m, $C_{(3)}$–H), 5.65 (m, $C_{(9)}$–H), and 7.08 (q, $J=1$ Hz, $C_{(12)}$–H); PMR (CS_2): δ 0.99 (d, $J=7$ Hz, $C_{(4)}$–CH_3), 1.06 (s, $C_{(5)}$–CH_3), 1.88 (d, $J=ca.$ 1 Hz, $C_{(11)}$–CH_3), 1.91 (s, $-OCOCH_3$), 2.00 (s, $-OCOCH_3$), 4.94(m, $C_{(3)}$–H), 5.48 (m, $C_{(9)}$–H), and 6.97 (q, $J=ca.$ 1 Hz, $C_{(12)}$–H); MS: *m/e* 350 [1%, M^+ ($C_{19}H_{26}O_6$)], 332 (3%, [M−H_2O]$^+$), 290 (3%, [M−CH_3COOH]$^+$), 230 (4%, [M−2CH_3COOH]$^+$), 166 (37%, *retro*-Diels-Alder fragment), 124 (100%), and 43 (36%, [CH_3CO]$^+$).

Reduction of ***5*** *with Lithium Aluminium Hydride.* To a suspension of lithium aluminium hydride (97 mg) in dry ether (3 ml) was added a solution of **5** (52 mg) in dry ether (3 ml) and the mixture was stirred for 3.5 h at room temperature under a nitrogen atmosphere. An excess of lithium aluminium hydride was decomposed by addition of water and the product was extracted with ether. The usual treatment of the extract gave a residue, which was chromatographed on silica gel (300 mg) using ether as eluent to afford 3*β*,9*β*,10*β*-trihydroxyfuranoeremophilane (**4**; 21 mg) and 3*β*,9*α*,10*β*-trihydroxyfuranoeremophilane (**12**; 27 mg). The latter compound (**12**) showed a higher R_f value than that of **4** on TLC (silica gel) developed with ether. The separated compound (**12**) without further purification was used for acetylation.

Acetylation of ***12*** *with Acetic Anhydride in Pyridine.* A solution of **12** (27 mg), acetic anhydride (0.2 ml), and pyridine (0.5 ml) was allowed to stand overnight at room temperature. After addition of methanol (1 ml), the solvent was removed under reduced pressure. The residual oil was subjected to separation by preparative TLC (developed with light petroleum–ether, 3:5) to give 3*β*,9*α*-diacetoxy-10*β*-hydroxyfuranoeremophilane (**13**; 18 mg; one spot on TLC), an oil, IR (Nujol): 3460, 1730, and 1560 cm^{-1}; PMR (CCl_4): δ 1.11 (d, $J=7$ Hz, $C_{(4)}$–CH_3), 1.11 (s, $C_{(5)}$–CH_3), 1.92 (d, $J=ca.$ 1 Hz, $C_{(11)}$–CH_3), 2.00 (s, $-OCOCH_3$), 2.19 (s, $-OCOCH_3$), 5.25 (m, $C_{(3)}$–H), 5.70 (m, $C_{(9)}$–H), and 7.05 (q, $J=ca.$ 1 Hz, $C_{(12)}$–H); PMR (CS_2): δ 1.00 (s, $C_{(5)}$–CH_3), 1.04 (d, $J=7$ Hz, $C_{(4)}$–CH_3), 1.86 (d, $J=ca.$ 1 Hz, $C_{(11)}$–CH_3), 1.90 (s, $-OCOCH_3$), 2.07 (s, $-OCOCH_3$), 5.08 (dt, $J=11$ Hz and $J=5$ Hz, $C_{(3)}$–H), 5.54 (s, $C_{(9)}$–H), and 6.93 (q, $J=ca.$ 1 Hz, $C_{(12)}$–H); MS: *m/e* 350 [1%, M^+ ($C_{19}H_{26}O_6$)], 332 (7%, [M−H_2O]$^+$), 290 (4 %, [M−CH_3COOH]$^+$), 230 (6%, [M−2CH_3COOH]$^+$),), 215 (9%), [M−2CH_3COOH—CH_3]$^+$), 166 (31%, *retro*-Diels-Alder fragment), 124 (100%), and 43 (71%, [CH_3CO]$^+$).

Alkaline Hydrolysis of ***2****.* A solution of potassium hydroxide (250 mg) in ethanol (5 ml) was added to **2** (37 mg) and the mixture was refluxed for 1 h under a nitrogen atmosphere. After the solvent was distilled off, the residue was recrystallized from ether to give colorless crystals, **14**, mp 153—154 °C (dec). This compound was found to be identical (mp, IR, PMR, and mass spectra) with **14**, obtained from **2** by treatment with lithium aluminium hydride (*vide infra*).

Reduction of ***2*** *with Lithium Aluminium Hydride.* To a suspension of lithium aluminium hydride (210 mg) in dry ether (6 ml), an oil (893 mg) containing **2** as the major component was added and stirred for 4 h at room temperature under a nitrogen atmosphere. An excess of lithium aluminium hydride was decomposed by addition of water and the product was extracted with ether. The ethereal solution was dried over anhydrous sodium sulfate and the solvent was evaporated to give a residue(519 mg), which was chromatographed on silica gel (30 g). Fractions 8—10 eluted with light petroleum–ether (1:1) (each fraction 50 ml) gave a crystalline product (129 mg), which was recrystallized from acetone–diisopropyl ether to afford 3*β*,10*β*-dihydroxyfuranoeremophilane (**14**), mp 151—153 °C, $[\alpha]_D^{21}$ −11° (*c* 1.0, MeOH). Spectral data of **14** are as follows; UV (MeOH): λ_{max} 220 nm (ε 5800); IR (Nujol): 3425, 1655, and 1560 cm^{-1}; PMR ($CDCl_3$): δ 1.10 (d, $J=7$ Hz, $C_{(4)}$–CH_3), 1.14 (s, $C_{(5)}$–CH_3), 1.89 (d, $J=1.5$ Hz, $C_{(11)}$–CH_3), 4.02 (m, $C_{(3)}$–H), and 7.03 (m, $C_{(12)}$–H); MS: *m/e* 250 [14%, M^+ ($C_{15}H_{22}O_3$)], 109 (100%), and 108 (62%, *retro*-Diels-Alder fragment). Found: C, 72.16; H, 8.68%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.68%.

Oxidation of ***14*** *with Chromium Trioxide in Pyridine.* To a solution of chromium trioxide (102 mg) in pyridine (6 ml) was added a solution of **14** (95 mg) in pyridine (2 ml) with stirring at 0 °C. The mixture was allowed to stand at room temperature for 2.5 h under a nitrogen atmosphere, diluted with a mixture of crashed ice and water, and extracted with ether. The extract was washed with water and dried over anhydrous sodium sulfate. The solvent was removed to give a residue (77 mg). From the residue **14** (14 mg) and **15** (47 mg) were separated by preparative TLC (developed with light petroleum–ether, 1 : 4). 10*β*-Hydroxy-3-oxofuranoeremophilane (**15**; one spot on TLC); an oil, $[\alpha]_D^{24}$ +10° (*c* 1.07, MeOH); UV (EtOH): λ_{max}219 nm (ε 4500); IR (neat): 3450, 1700, 1645, and 1560 cm^{-1}; PMR (CCl_4): δ 0.92 (s, $C_{(5)}$–CH_3), 0.94 (d, $J=7$ Hz, $C_{(4)}$–CH_3), 1.87 (d, $J=1.5$ Hz, $C_{(11)}$–CH_3), and 6.96 (m, $C_{(12)}$–H); MS: *m/e* 248 [<5%, M^+ ($C_{15}H_{20}O_3$)] and 108 (100%, *retro*-Diels-Alder fragment).

Deuterium-exchange Reaction of ***15****.* A solution of **15** (25 mg) in CH_3OD (1 ml) was warmed at 70 °C in the presence of a trace of NaOD for 10 h in a sealed tube. The reaction mixture was diluted with water and the extracted with ether. The extract was washed with dilute hydrochloric acid, water, aqueous solution of sodium hydrogencarbonate, and then with water. The ethereal solution was dried over anhydrous sodium sulfate and the solvent was evaporated to give a residue. The residue was submitted once more to deuterium-exchange reaction in a similar manner. The resulting oil was purified by preparative TLC to afford a mixture of **15**-d_3 and **15′**-d_3(1: 5). This mixture showed one spot on TLC developed with light petroleum–ether (1: 1). Signals due to **15′**-d_3 in the PMR spectrum of the mixture are as follows; δ (CCl_4) 1.01 (s, $C_{(4)}$–CH_3), 1.04 (s, $C_{(5)}$–CH_3), 1.84 (d, $J=1.5$ Hz, $C_{(11)}$–CH_3), and 6.92 (m, $C_{(12)}$–H). Treatment of the mixture with sodium hydroxide in methanol gave a mixture of **15** and 10*β*-hydroxy-3-oxo-4*βH*-furanoeremophilane (**15′**), whose PMR spectra show a doublet due to the C-4 methyl in **15′** at δ (CCl_4) 1.00 (d, $J=7$ Hz) and δ (C_6H_6) 1.05 (d, $J=7$ Hz).

Reduction of ***11*** *with Lithium in Ethylamine.* To a solution of **11** (123 mg) in ethylamine (10 ml) cooled to −78 °C

was added lithium (80 mg) and the reaction mixture was stirred at this temperature. When the reaction mixture changed to blue in color saturated aqueous solution of ammonium chloride (10 ml) was added. The resulting solution was extracted with ether for three times and a combined ethereal solution was washed with dilute hydrochloric acid, water, and with saturated brine, and dried over anhydrous sodium sulfate. The crude product (65 mg) was chromatographed on silica gel (6 g). Elution with hexane–ether (1:1; 200 ml) yielded 3β,10β-dihydroxyfuranoeremophilane (**14**; 36 mg), mp 152—154 °C (recrystallization from acetone–diisopropyl ether), $[\alpha]_D^{28}$ −9° (*c* 1.3, MeOH), IR (Nujol): 3425 cm^{-1}; PMR ($CDCl_3$): δ 1.10 (d, J=7 Hz, $C_{(4)}$–CH_3), 1.15 (s, $C_{(5)}$–CH_3), 1.90 (d, J=*ca.* 1 Hz, $C_{(11)}$–CH_3), 4.02 (m, $C_{(3)}$–H), and 7.05 (m, $C_{(12)}$–H); MS: *m/e* 250 [10%, M^+ ($C_{15}H_{22}O_3$)], 109 (100%), and 108 (64%, *retro*-Diels-Alder fragment). This compound was found to be identical (mp, $[\alpha]_D$ IR, PMR, and mass spectra) with **14** prepared from **2**.

*Application of the Horeau's Method to **14**.* A solution of **14** (14 mg, 0.056 mmol) in pyridine (0.3 ml) was allowed to stand overnight with α-phenylbutyric anhydride (67.7 mg, 0.218 mmol) at room temperature. The reaction mixture was treated by a similar manner described above. Esterification 100%; optical yield (−) 28% (optical rotation α_D −0.027°, cell length 0.1 dm, benzene solution 1.5 ml).

*Acetylation of **14** with Acetic Anhydride in Pyridine.* A mixture of **14** (22 mg), acetic anhydride (0.5 ml), and pyridine (4 ml) was allowed to stand overnight at room temperature. After addition of methanol the solvent was evaporated under reduced pressure to afford a residue. The residue was passed through a silica gel column (2 g) (light petroleum–ether, 10:1) to give **16** (one spot on TLC), an oil, IR (neat): 3450 and 1735 cm^{-1}; PMR (CS_2 at 30 °C): δ 1.00 (d, J= 8 Hz, $C_{(4)}$–CH_3), 1.04 (s, $C_{(5)}$–CH_3), 1.88 (d, J=*ca.* 1 Hz, $C_{(11)}$–CH_3), 1.97 (s, –$OCOCH_3$), 5.06 (quintet, J=4 Hz, $C_{(3)}$–H), and 6.94 (m, $C_{(12)}$–H); MS: *m/e* 292 [7%, M^+ ($C_{17}H_{24}O_4$)], 206 (76%), 109 (80%), 108 (51%, *retro*-Diels-Alder fragment), and 43 (100%, $[CH_3CO]^+$).

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