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# Studies on the Terpenoids and Related Alicyclic Compounds. XXX.[1,2] An Application of the Angular Hydroxylation Using Benzeneseleninic Anhydride to the Syntheses of 10β-Hydroxyfuranoeremophilane Derivatives

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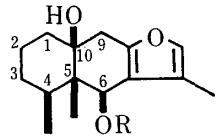
The syntheses of several 10β-hydroxyfuranoeremophilane derivatives, (±)-10β-hydroxyfuranoeremophilane-3,6-dione (**3**), (±)-10β-hydroxyfuranoeremophilan-6-one (**4**), and (±)-10β-hydroxy-6β-isobutyryloxyfuranoeremophilan-9-one (**5**), are described. The key step in these syntheses is the angular hydroxylation of 10βH-furanoeremophilane-6,9-dione (**6**) using benzeneseleninic anhydride. Reduction of the 10β-hydroxy-6,9-dione (**7**) with $NaBH_4$ or Zn–$NH_4OH$ gave the 9α- or 9β-hydroxy compounds (**9a** and **10**), respectively. The stereochemistries of the diols (**9a** and **10**) were confirmed by the chemical conversion of **9a** to the known compound **17**. Treatment of **9a** and **10** with methanesulfonyl chloride–$Et_3N$ afforded the 9β,10β-epoxide (**18**). Ring-opening of **18** with $NaBH_4$ gave the 10β-hydroxy compound (**21**). Deacetalization of **21** with aq. acetic acid afforded (±)-**3**. Desulfurization of the 3,3-dithioacetal (**24**) which was derived from **21** with Raney Ni gave (±)-**4**. The enone (**27a**) was treated with isobutyric anhydride followed by catalytic reduction to afford **28b** as a major product. Hydroxylation of **28** with benzeneseleninic anhydride in the presence of NaH in chlorobenzene afforded the 10β- and 10α-hydroxy compounds (**29a** and **29b**). Desulfurization of the 3,3-dithioacetal of **30a** which was derived from **29a** with Raney Ni gave (±)-**5**.

**Keywords**——hydroxylation; benzeneseleninic anhydride; sesquiterpene; 10β-hydroxyfuranoeremophilane; synthesis

Recently, Takahashi and his coworkers[3,4] have isolated a number of furanoeremophilanes from *Ligularia* and other related species. Further, Bohlmann *et al.*[5] reported that a number of highly oxygenated furanoeremophilanes have been isolated from plants belonging to *Europs, Senecio* and *Othonna* (Senecioneae). 6β,10β-Dihydroxyfuranoeremophilane, tetradimodiol (**1a**), and its 6β-esters (**1b**—**1h**) were isolated from *Ligularia japonica* LESS,[3] *Farfugium japonicum* KITAMURA,[4] *Othonna amplexicaulis* THUNB,[5] and *Tetradymia gla-*



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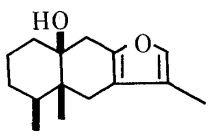
**a** : R=H[3,6]
**b** : R=$CH_3$[3]
**c** : R=angeloyl[5]
**d** : R=tigloyl[5]
**e** : R=senecioyl[4]
**f** : R=2-methylbutanoyl[3]
**g** : R=isovaleroyl[5]
**h** : R=isobutyroyl[6]



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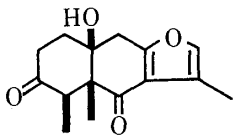

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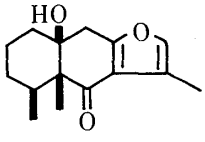

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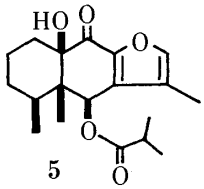

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*brata*.[6] 10β-Hydroxyfuranoeremophilane, tetradymol (**2**),[7] was also isolated from *T. glabrata*. These compounds, **1a** and **2**, were shown to be one of the hepatotoxic and cardiac failure-inducing substances responsible for the death of sheep feeding on the plant.[5,6]

The authors have recently reported[8] the introduction of a hydroxyl group into the angular position of polycyclic ketone derivatives using benzeneseleninic anhydride, $(PhSeO)_2O$. In connection with studies on the total synthesis of highly oxygenated furanoeremophilanes[9] we wish to report here, in detail, an application of this angular hydroxylation to the syntheses of 10β-hydroxyfuranoeremophilane-3,6-dione (**3**),[10] 10β-hydroxyfuranoeremophilan-6-one (**4**),[3b] and 10β-hydroxy-6β-isobutyryloxyfuranoeremophilan-9-one (**5**).[11]

**Syntheses of (±)-10β-Hydroxyfuranoeremophilane-3,6-dione and (±)-10β-Hydroxyfuranoeremophilan-6-one**

The hydroxylation of 3,3-ethylenedioxyfuranoeremophilane-6,9-dione (**6**)[12] with $(PhSeO)_2O$ gave the 10β-hydroxy compound (**7**) and the 10α-epimer (**8**) in 57 and 17% yields, respectively, as reported previously.[8] Some attempts to synthesize the target compounds (**3** and **4**) were made by reductive deoxygenation of the C-9 carbonyl group of **7**. Reduction of **7** with sodium borohydride ($NaBH_4$) gave the 9-hydroxy-6-one (**9a**) quantitatively, as described in the previous paper.[9] Wynberg *et al.*[13] reported that reduction of some aryl ketones with zinc dust in the presence of $CuSO_4$ in aq. $NH_4OH$ gave the corresponding aryl methylene compound. Reduction of **7** with zinc dust according to Wynberg's procedure gave a new ketol (**10**),[14] mp 223—225 °C, together with a hydrogenolysis product (**11**),[12] in 56 and 20% yields, respectively, but treatment of **10** with zinc dust under the same conditions did not give the ketol (**11**). Thus, we presumed that hydrogenolysis of **7** initially gave the diketone (**6**) as an intermediate, and then reduction of **6** yielded the ketol (**11**).

The stereochemistry of both diols (**9a** and **10**) was investigated. The ultraviolet (UV) spectra of **9a** and **10** showed the same $\lambda$ maximum at 266 nm, which is due to the 6-oxofuranoeremophilane moiety.[15] Oxidation of both **9a** and **10** with activated $MnO_2$ afforded the same diketone (**7**). Therefore **9a** and **10** should be epimeric 9-hydroxy derivatives. The ketols (**9a** and **10**) were previously assumed to be 9β- and 9α-hydroxy epimers, respectively,[9,14] but these assignments have been revised to the 9α- and 9β-hydroxy epimers, respectively, on the basis of the chemical conversion of **9a** to the known 10α-hydroxytriketone (**17**).[9]

Allylic epoxidation of the 9-hydroxy-1,10-dehydro compound (**12**), which was formed from **9a** in three steps as described in the previous paper,[9] with *tert*-butyl hydroperoxide in the presence of vanadyl acetylacetonate under Itoh's condition[16] afforded the 9-hydroxy-1,10-epoxide (**13**), mp 168—170 °C, together with the known diketone (**14**)[9] in 70 and 30% yields, respectively. As Sharpless's method was used in this step, the configurations of the epoxy ring and 9-hydroxyl group should be the same. Oxidation of **13** with activated $MnO_2$ gave a diketone (**15**) in 95% yield. When treated with aq. acetic acid at 60 °C, **15** underwent hydrolysis and β-elimination simultaneously to form the 10-hydroxy enone (**16**), mp 197—198 °C, in 72% yield. Catalytic reduction of **16** with Pd charcoal under an $H_2$ atmosphere gave the known 10α-hydroxyfuranoeremophilane-3,6,9-trione (**17**),[9] quantitatively. From these chemical correlation results, the diols **9a** and **10** were determined to be the *trans*-9α,10β-diol and *cis*-9β,10β-diol, respectively.

Treatment of **9a** with methanesulfonyl chloride in triethylamine at room temperature for 24 h gave the 9β,10β-epoxide (**18**), mp 123—124 °C, in 81% yield. The epoxide (**18**) was also formed (83% yield) from **10** under the same conditions. The epoxide (**18**) showed the molecular ion *m/z* 304.1307 corresponding to $C_{17}H_{20}O_5$, in its mass spectrum. Ring-opening

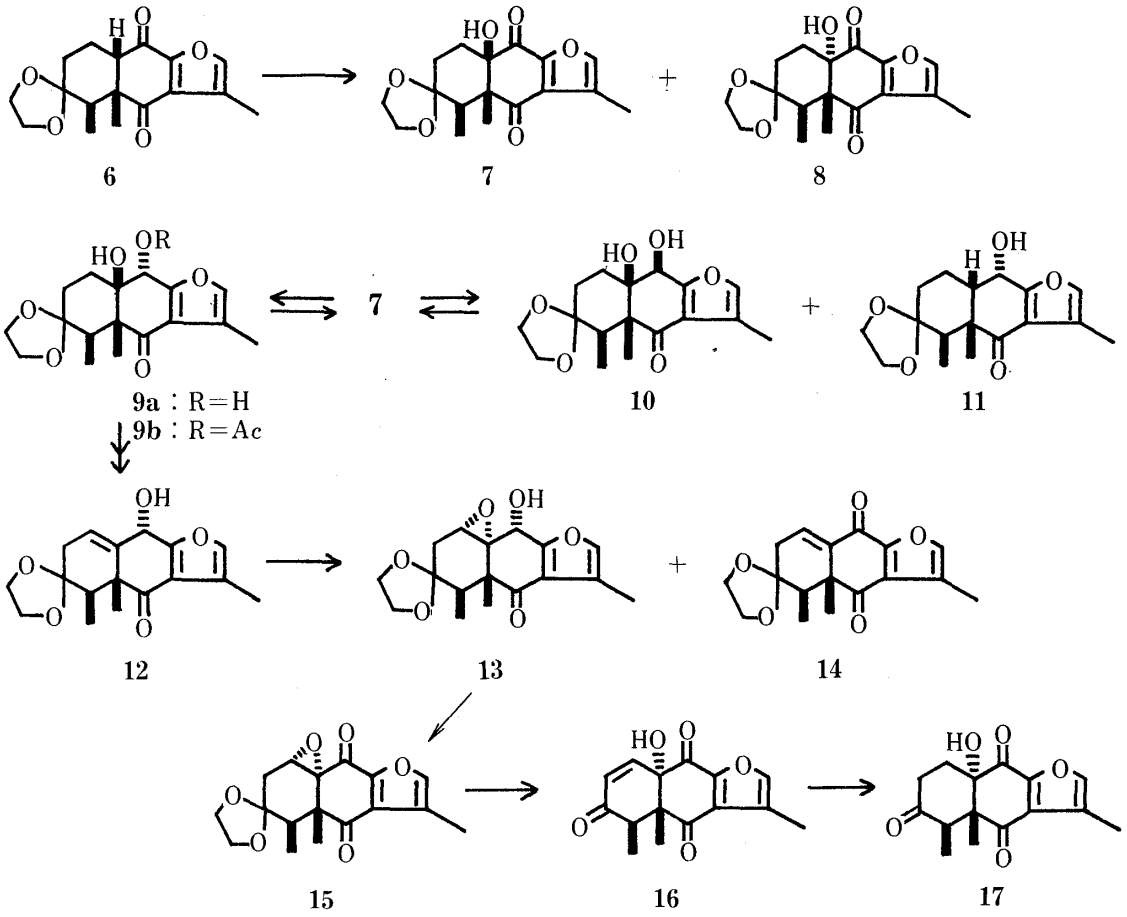


Chart 1

reactions of the 9β,10β-epoxide of **18** with metal hydrides or some nucleophilic reagents were investigated. Treatment of **18** with lithium aluminum hydride ($LiAlH_4$) gave a complex mixture, in which no furan compound was detected. Treatment of **18** with freshly prepared sodium phenylselenate, prepared from diphenyl diselenide and $NaBH_4$,[17] did not give the expected phenylselenenohydrin (**19**). However, a phenylselenide (**20**), mp 135.5—136 °C, together with a 10β-hydroxy compound (**21**), as an oil, were formed in 88 and 12% yields, respectively. The UV spectrum of **20** showed λ maximum at 330.5 nm, which was consistent with that of the known 9,10-dehydro-3β-hydroxyfuranoeremophilan-6-one (**22**).[18] The high-resolution in-beam mass spectrum (IB-MS) of **20** showed the molecular ion at *m/z* 444.0809, corresponding to $C_{23}H_{24}O_4Se$. From these spectral data, the phenylselenide was shown to be a dehydrated product (**20**). The mechanism of the formation of **20** is assumed to involve removal of the C-9 hydrogen of the initial product (**19**) by the base followed by β-elimination, as illustrated in Chart 2.

The structure of the by-product (**21**) was deduced from the spectroscopic data [high-resolution IB-MS: *m/z* 306.1432 ($C_{17}H_{22}O_5$) and IR $\nu$ 3450 $cm^{-1}$ (OH)]. When the epoxide (**18**) was treated with an excess amount of sodium phenylselenate, the yield of **21** increased (87%). Therefore, $NaBH_4$ was regarded as the real reactant. Treatment of **18** with $NaBH_4$ indeed gave **21** in 62% yield together with unchanged **18** in 35% yield.

Deacetalization of **21** with aq. acetic acid gave (±)-**3**, mp 188—188.5 °C, in 71% yield. The infrared (IR), UV, and nuclear magnetic resonance (NMR) spectra of (±)-**3** were in good agreement with those of 10β-hydroxyfuranoeremophilane-3,6-dione which was derived from natural nemosenin-A (**23**), as reported by Novotny *et al.*[10]

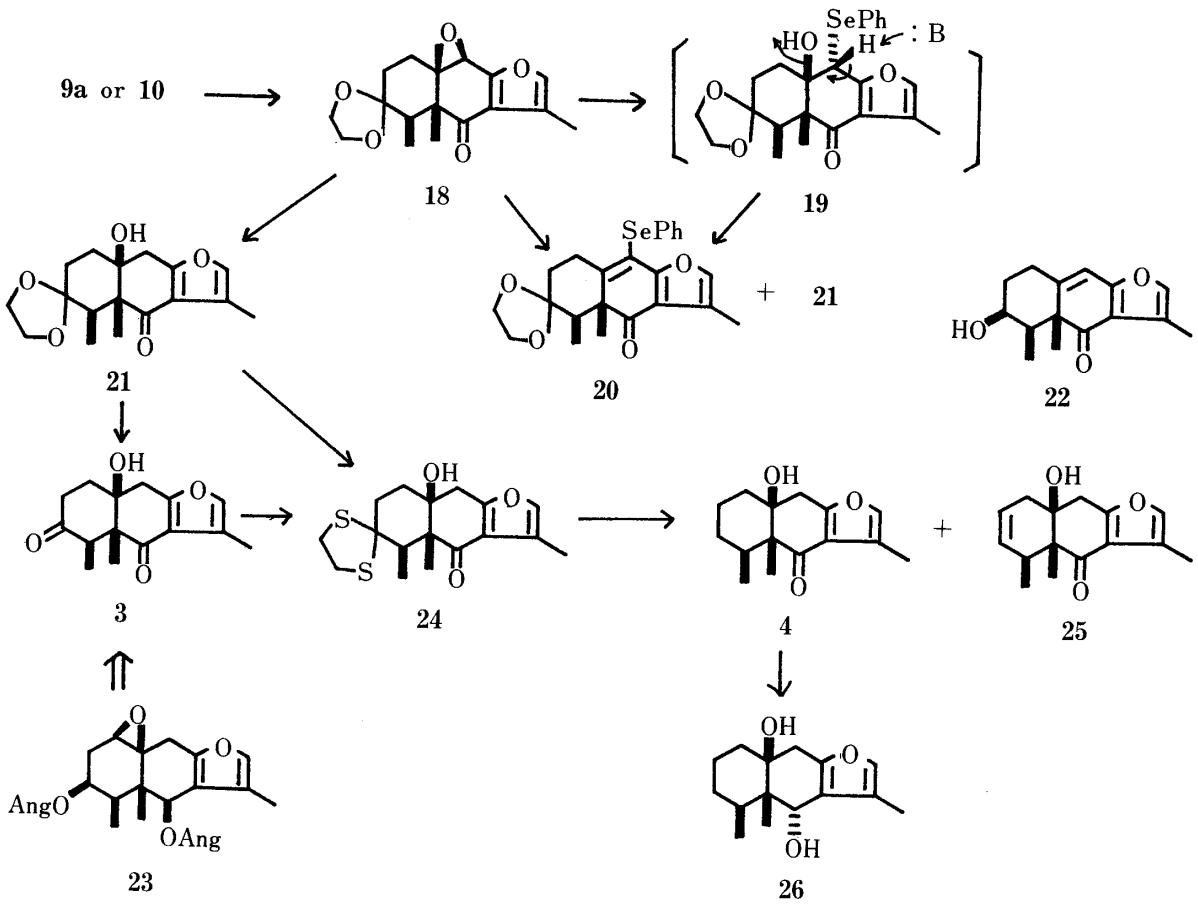


Chart 2

Treatment of the 3,3-ethylenedioxy acetal (**21**) with excess ethanedithiol in the presence of a catalytic amount of $BF_3$–$OEt_2$ complex in methylene chloride afforded the 3,3-ethylenedithio acetal derivative (**24**), mp 179—180 °C, in 77% yield. Reductive desulfurization of **24** with Raney Ni (W-2) in refluxing ethanol gave (±)-**4**, mp 120—121 °C, in 71% yield together with a dehydro compound (**25**), as an oil, in 5% yield. The spectral data of (±)-**4** were in good agreement with those of 10β-hydroxyfuranoeremophilan-6-one which was derived from natural tetradimodiol by $CrO_3$ oxidation, as reported by Tada *et al.*[3]

Attempted synthesis of tetradimodiol (**1a**) from (±)-**4** under various conditions was unsuccessful, resulting in decomposition or recovery of the starting material. In the case of reduction of **4** with $LiAlH_4$, only 6-epitetradimodiol (**26**) was obtained as an unstable oil.

**Synthesis of 10β-Hydroxy-6β-isobutyryloxyfuranoeremophilan-9-one**

10β-Hydroxy-6β-isobutyryloxyfuranoeremophilan-9-one (**5**) was obtained as a reduction product of natural senmauricinolisobutyrate (**32**) as reported by Bohlmann *et al.*[11] Compound (**5**) possesses 6β-ester and 10β-hydroxyl groups, as tetradimodiol (**1a**) and its ester derivatives (**1b**—**1h**) do. As a continuation of the synthetic studies on 10β-hydroxyfuranoeremophilanes, synthesis of **5** was investigated starting from the enone (**27a**).[9] The enone (**27a**) was treated with isobutyric anhydride and pyridine to give the isobutyrate (**27b**), as an oil, in 93% yield. Catalytic reduction of **27b** with Pd on charcoal catalyst under an $H_2$ atmosphere afforded **28a**, mp 129.5—131 °C, and **28b**, as an oil, in 22 and 72% yields, respectively. The stereochemistry of the hydrogen at the angular position (C-10) of these compounds (**28a** and **28b**) was assumed to be 10β and 10α, respectively, since catalytic reduction of **33** gave the 10αH product as a major product.[9]

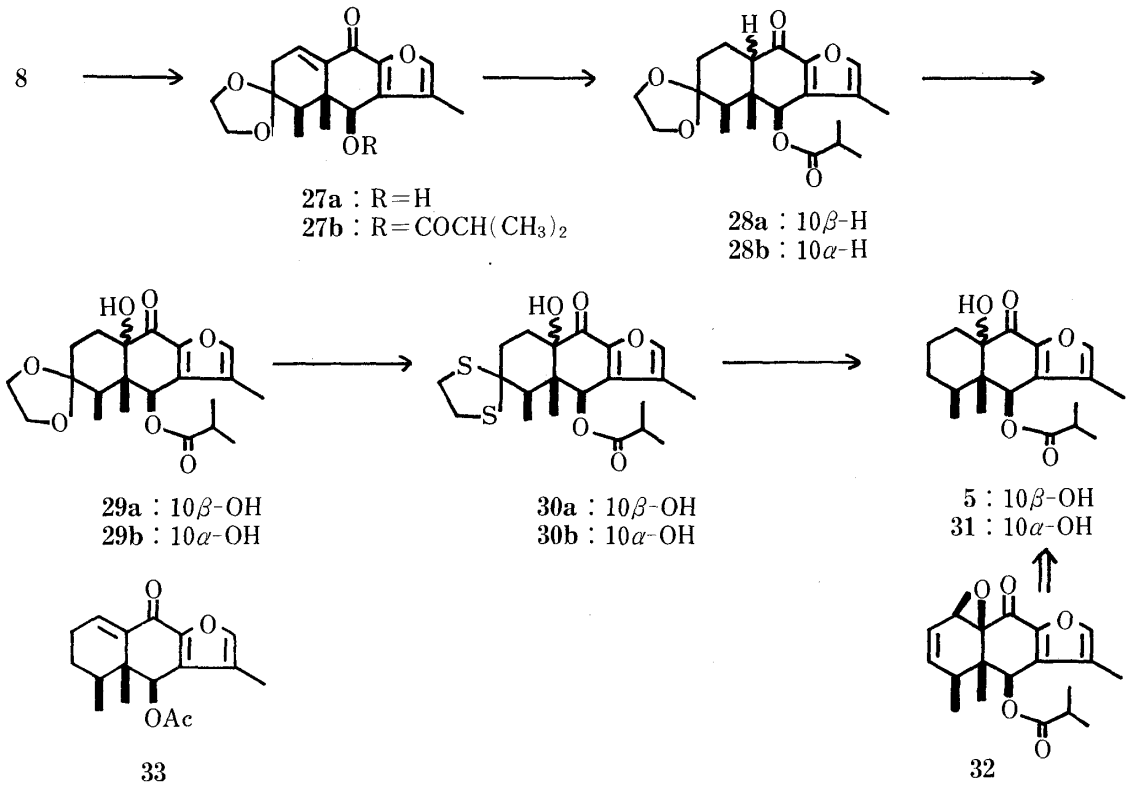


Chart 3

Hydroxylation of the major compound (**28b**) was carried out with $(PhSeO)_2O$ in refluxing chlorobenzene in the presence of 1.5 equivalents of sodium hydride (NaH) to give the 10$\beta$-hydroxy compound (**29a**), mp 123.5—126 °C, and the 10$\alpha$-hydroxy epimer (**29b**), as an oil, in 45 and 40% yields, respectively. When the hydroxylation was carried out in the absence of NaH, a complex mixture was obtained. Treatment of the 10$\beta$-H epimer (**28a**) with $(PhSeO)_2O$ in the presence of NaH under the same conditions as used for **28b** gave a similar mixture of **29a** and **29b**. We observed that a number of 10$\beta$-hydroxyfuranoeremophilane derivatives showed much larger *Rf* values on silica gel thin layer chromatographic plates than the corresponding 10$\alpha$-epimers. The *Rf* value of **29a** on a silica gel TLC plate was much larger than that of **29b**, so the hydroxyl groups of **29a** and **29b** are assumed to be 10$\beta$ and 10$\alpha$, respectively. The structure of **29a** was finally confirmed by transforming it to **5**.

The dioxy acetals (**29a** and **29b**) were converted to the dithio acetals **30a** (87% yield) and **30b** (83% yield), respectively, by treatment with ethanedithiol in the presence of $BF_3$–$OEt_2$ complex. Reductive desulfurization of **30a** with Raney Ni in refluxing ethanol gave (±)-**5**, mp 153—157 °C, in 39% yield. The NMR spectrum of (±)-**5** was identical with that of 10$\beta$-hydroxy-6$\beta$-isobutyryloxyfuranoeremophilan-9-one reported by Bohlmann *et al.*[11] On the other hand, reductive desulfurization of **30b** with Raney Ni under the same conditions gave (±)-**31**, the C-10 epimer of **5**, mp 190—193 °C, in 42% yield.

From these studies, it was established that the angular hydroxylation using benzeneseleninic anhydride is an effective oxidation method for the synthesis of highly oxygenated furanoeremophilanes.

## Experimental

All melting points are uncorrected. IR spectra were measured in KBr disks with a Hitachi 215 spectrometer. UV spectra were measured with a Hitachi 200 spectrometer. NMR spectra were measured in $CDCl_3$ solution on a JEOL

JNM-FX-100 pulse Fourier transform spectrometer (100 MHz) using $Me_4Si$ as an internal standard. Electron impact and in-beam mass spectra (EI-MS and IB-MS) were taken on a Hitachi M-80 double focusing spectrometer at 70 eV by direct insertion. High-resolution mass spectra were determined with a Hitachi datalyser 003 system connected on-line with the mass spectrometer. Wako silica gel C-200 (200 mesh) containing 2% fluorescence reagent 254 was used in column chromatography. Preparative thin-layer chromatography (TLC) was carried out using Merck silica gel $HF_{254}$.

**3,3-Ethylenedioxy-9β,10β-dihydroxyfuranoeremophilan-6-one (10)**——A suspension of 34 mg of the diketone (**7**), Zn dust (80 mg), and $CuSO_4$ (1 mg) in 2 ml of 29% $NH_4OH$ was refluxed and 1 ml of $NH_4OH$ was added every 3 h. Refluxing was continued for 18 h and then the reaction mixture was extracted with AcOEt. The products were separated by silica gel preparative TLC to give 19 mg (56%) of **10** and 6.5 mg (20%) of **11**. **10**: mp 223—225 °C; High-resolution mass spectrum for $C_{17}H_{22}O_6$: Mol. Wt. 322.1415. Observed: $M^+$, 322.1434. IR $cm^{-1}$: 3430 (OH), 1675, 1650 (CO); UV $\lambda_{max}^{EtOH}$ 266 nm; NMR $\delta$: 0.84 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.34 (3H, s, 5-$CH_3$), 2.19 (3H, d, $J$=1 Hz, 11-$CH_3$), 3.6—4.1 (4H, m, $\begin{matrix}CH_2O\\CH_2O\end{matrix}>$), 5.13 (1H, br s, 9-H), 7.15 (1H, q, $J$=1 Hz, 12-H); MS $m/z$ (% rel. int.): 322 ($M^+$, 2), 306 (7), 138 (10), 99 (100).

**$MnO_2$ Oxidation of the Diols (9a) and (10)**——a) From Diol (**9a**): Activated $MnO_2$ (100 mg) was added to a solution of 13 mg of **9a** in 2 ml of tetrahydrofuran (THF) and the reaction mixture was stirred at room temperature for 40 min. The $MnO_2$ was filtered off and the filtrate was concentrated *in vacuo*. The products were separated by silica gel preparative TLC to afford 7 mg (54%) of the diketone (**7**) and 3 mg (23%) of the starting material (**9a**).

b) From Diol (**10**): Diol (**10**) (7.4 mg) was oxidized with activated $MnO_2$ (100 mg) in 2 ml of THF in the same manner as described above to afford 2.3 mg (31%) of the diketone (**7**) and 1.5 mg (20%) of the starting material (**10**).

**Epoxidation of the Allylic Alcohol (12)**——According to the procedure reported by Itoh,[16] 45 μl of 70% *tert*-butyl hydroperoxide solution was added to a solution of 50 mg of the allylic alcohol (**12**) and 3 mg of VO $(acac)_2$ in 3 ml of benzene at room temperature and the reaction mixture was stirred for 30 min. A small amount of VO $(acac)_2$ was added and the stirring was continued for another 30 min. The reaction mixture was filtered through a short column of florisil and the filtrate was evaporated to dryness. The products were separated by silica gel preparative TLC to give 15 mg (30%) of the known diketone (**14**) and 37 mg (70%) of the epoxide (**13**). Recrystallization of **13** from AcOEt–hexane gave colorless prisms, mp 168—170 °C; High-resolution mass spectrum for $C_{17}H_{20}O_6$: Mol. Wt. 320.1254. Observed: $M^+$ 320.1267. IR $cm^{-1}$: 3500 (OH), 1685 (CO); UV $\lambda_{max}^{EtOH}$ 266.5 nm (ε 3300); NMR $\delta$: 1.15 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.48 (3H, s, 5-$CH_3$), 2.18 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.45 (1H, q, $J$=7 Hz, 4-H), 3.59 (1H, dd, $J$=4.5, 1 Hz, 1-H), 3.7—4.2 (4H, m, $\begin{matrix}CH_2O\\CH_2O\end{matrix}>$), 5.18 (1H, d, $J$=12 Hz, 9-H, $+D_2O$ gave singlet), 7.16 (1H, q, $J$=1 Hz, 12-H); MS $m/z$ (% rel. int.): 320 ($M^+$, 100), 303 (55), 291 (74), 155 (98).

**1α,10α-Epoxy-3,3-ethylenedioxyfuranoeremophilane-6,9-dione (15)**——A solution of **13** (34 mg) in 4 ml of $CHCl_3$ was stirred with 172 mg of activated $MnO_2$ at room temperature for 15 min. The $MnO_2$ was filtered off and the filtrate was evaporated to dryness *in vacuo*. The product was purified by silica gel preparative TLC to give 33 mg (95%) of **15**, mp >300 °C (colorless prisms from AcOEt–hexane). High-resolution mass spectrum for $C_{17}H_{18}O_6$: Mol. Wt. 318.1098. Observed: $M^+$ 318.1096. IR $cm^{-1}$: 1695 (CO); UV $\lambda_{max}^{EtOH}$ 306.5 nm (ε 9600); NMR $\delta$: 1.15 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.56 (3H, s, 5-$CH_3$), 2.27 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.55 (1H, q, $J$=7 Hz, 4-H), 3.7—4.1 Hz (5H, m, $\begin{matrix}CH_2O\\CH_2O\end{matrix}>$, and 1-H), 7.48 (1H, q, $J$=1 Hz, 12-H); MS $m/z$ (% rel. int.): 318 ($M^+$, 58), 289 (100).

**10α-Hydroxy-$\Delta^{1,2}$-furanoeremophilane-3,6,9-trione (16)**——A solution of 32 mg of **15** in 5 ml of 75% aq. AcOH was heated at 60 °C for 3 h. The solvent was evaporated off and the residue was purified by silica gel preparative TLC to give 20 mg (72%) of the enone (**16**), mp 197—198 °C (colorless prisms from AcOEt–hexane). High-resolution mass spectrum for $C_{15}H_{14}O_5$: Mol. Wt. 274.0837. Observed: $M^+$ 274.0835. IR $cm^{-1}$: 3350 (OH), 1700, 1670 (CO), 1635 (C=C); UV $\lambda_{max}^{EtOH}$ 304.5 nm (ε 8900); NMR $\delta$: 1.19 (3H, s, 5-$CH_3$), 1.49 (3H, d, $J$=7 Hz, 4-$CH_3$), 2.28 (3H, d, $J$=1 Hz, 11-$CH_3$), 3.47 (1H, q, $J$=7 Hz, 4-H), 6.24 (1H, d, $J$=10 Hz, 2-H), 7.51 (1H, d, $J$=10 Hz, 1-H), 7.52 (1H, q, $J$=1 Hz, 12-H); MS $m/z$ (% rel. int.): 274 ($M^+$, 22), 229 (55), 108 (70), 52 (100).

**10α-Hydroxyfuranoeremophilane-3,6,9-trione (17)**——Catalytic reduction of **16** (17.7 mg) in 2 ml of AcOEt with 6 mg of 10% Pd-C was carried out under an $H_2$ atmosphere at room temperature for 15 min. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo* to give 17 mg (96%) of crystalline product (**17**). Recrystallization of **17** from AcOEt–hexane gave colorless prisms, mp 224—247 °C (sublim.). The IR, UV, and NMR spectra of **17** were superimposable upon those of the known trione (**17**) reported previously.[9]

**9β,10β-Epoxy-3,3-ethylenedioxyfuranoeremophilan-6-one (18)**——a) From the Diol (**9a**): A solution of methanesulfonyl chloride (1.52 ml) in $CH_2Cl_2$ (3 ml) was added dropwise to a solution of **9a** (286 mg) in 9 ml of $CH_2Cl_2$ and 12.5 ml of $Et_3N$ with stirring under an $N_2$ atmosphere. The reaction mixture was stirred at room temperature overnight, then sat. aq. $NaHCO_3$ was added to decompose the excess methanesulfonyl chloride, and the whole mixture was extracted with ether. The product was separated by silica gel column chromatography to give 219 mg (81%) of the epoxide (**18**). Recrystallization of **18** from AcOEt–hexane gave pale yellow prisms, mp 123—124 °C; *Anal.* Calcd for $C_{17}H_{20}O_5$: C, 67.11; H, 6.58; Mol. Wt. 304.1305. Found: C, 67.09; H, 6.69; $M^+$ 304.1307. IR $cm^{-1}$:

1675 (CO); UV $\lambda_{max}^{EtOH}$ 278.5 nm ($\varepsilon$ 3400); NMR $\delta$: 0.85 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.46 (3H, s, 5-$CH_3$), 2.15 (3H, d, $J$=1 Hz, 11-$CH_3$), 3.7—4.2 (5H, m, $\overset{CH_2O}{\underset{CH_2O}{}}>$, and 9-H), 7.14 (1H, q, $J$=1 Hz, 12-H); MS $m/z$ (% rel. int.): 304 ($M^+$, 42), 275 (51), 99 (100).

b) From the Diol (**10**): A solution of **10** (25 mg) in 0.5 ml of $CH_2Cl_2$ and 0.5 ml of $Et_3N$ was treated dropwise with 51 $\mu$l of methanesulfonyl chloride under an $N_2$ atmosphere at 22 °C with stirring. The reaction mixture was stirred at that temperature for 20 h and then sat. aq. $NaHCO_3$ was added. The same work-up as described above gave 19.6 mg (83%) of the epoxide (**18**).

**Treatment of the Epoxide (18) with Sodium Phenylselenate**——A solution of 52 mg of **18** in a small amount of EtOH was added to a solution of sodium phenylselenate (prepared from 30 mg of diphenyl diselenide and 49 mg of $NaBH_4$ in 3 ml of EtOH).[17] The reaction mixture was refluxed for 30 min, then the solvent was evaporated off and the residue was extracted with ether. The products were separated by silica gel preparative TLC to give 69 mg (88%) of **20** and 6.3 mg (12%) of **21**. **20**: Pale yellow prisms (from AcOEt–hexane); mp 135.5—136 °C; High-resolution mass spectrum for $C_{23}H_{24}O_4Se$: Mol. Wt. 444.0837. Observed: $M^+$ 444.0809. IR $cm^{-1}$: 1650 (CO); UV $\lambda_{max}^{EtOH}$ 330.5, 248.5 nm; NMR $\delta$: 1.16 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.44 (3H, s, 5-$CH_3$), 2.21 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.61 (1H, ddd, $J$=14, 14, 6 Hz, 1-H), 3.49 (1H, ddd, $J$=14, 6, 3 Hz, 1-H), 3.7—4.2 (4H, m, $\overset{CH_2O}{\underset{CH_2O}{}}>$), 7.02 (1H, q, $J$=1 Hz, 12-H), 7.0—7.4 (5H, m, aromatic protons). **21**: Colorless oil; High-resolution mass spectrum for $C_{17}H_{22}O_5$: Mol. Wt. 306.1461. Observed: $M^+$ 306.1432. IR $cm^{-1}$: 3450 (OH), 1660 (CO); NMR $\delta$: 0.89 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.26 (3H, s, 5-$CH_3$), 2.19 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.86 (1H, d, $J$=18 Hz, 9-H), 3.35 (1H, d, $J$=18 Hz, 9-H), 3.7—4.1 (4H, m, $\overset{CH_2O}{\underset{CH_2O}{}}>$), 7.05 (1H, q, $J$=1 Hz, 12-H); MS $m/z$ (% rel. int.): 306 ($M^+$, 68), 288 (24), 99 (100).

**Reduction of the Epoxide (18) with $NaBH_4$**——A solution of 340 mg of **18** in 35 ml of 98% EtOH was treated with 162 mg of $NaBH_4$ and the reaction mixture was refluxed for 1 h. Crystalline $NH_4Cl$ was added to the mixture and the solvent was evaporated off *in vacuo*. The residue was extracted with AcOEt. The product was separated by silica gel column chromatography to afford **21** (211 mg; 62%) along with the starting material (**18**) (119 mg; 35%).

**(±)-10β-Hydroxyfuranoeremophilane-3,6-dione (3)**——A solution of **21** (46 mg) in 4 ml of 75% aq. AcOH was refluxed for 4 h. The aq. AcOH was evaporated off and the residue was purified by silica gel preparative TLC to give 28 mg (71%) of (±)-3, mp 188—188.5 °C, as colorless prisms (recrystallized from AcOEt–hexane). High-resolution mass spectrum for $C_{15}H_{18}O_4$: Mol. Wt. 262.1200. Observed: $M^+$ 262.1146. IR $cm^{-1}$ ($CHCl_3$): 3600 (OH), 1710, 1670 (CO); UV $\lambda_{max}^{EtOH}$ 269 nm ($\varepsilon$ 3100); NMR $\delta$: 0.87 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.12 (3H, s, 5-$CH_3$), 2.19 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.66 (1H, q, $J$=7 Hz, 4-H), 3.05, 3.77 (each 1H, d, $J$=18 Hz, 9-H), 7.12 (1H, q, $J$=1 Hz, 12-H); MS $m/z$ (% rel. int.): 262 ($M^+$, 45), 226 (10), 122 (100).

**3,3-Ethylenedithio-10β-hydroxyfuranoeremophilan-6-one (24)**——a) From the Ketal (**21**): A mixture of **21** (25 mg), ethanedithiol (500 $\mu$l) and $BF_3$–$OEt_2$ (3 drops) in 2 ml of $CH_2Cl_2$ was stirred at room temperature for 5 h, then excess sat. aq. $NaHCO_3$ was added and the whole mixture was extracted with ether. The ether layer was washed once with sat. brine. The product was purified by silica gel column chromatography to give 21.3 mg (77%) of **24**, mp 179—180 °C, as colorless prisms (from AcOEt–hexane). High-resolution mass spectrum for $C_{17}H_{22}O_3S_2$: Mol. Wt. 338.1005. Observed: $M^+$ 338.1004. IR $cm^{-1}$: 3425 (OH), 1650 (CO); UV $\lambda_{max}^{EtOH}$ 267 nm ($\varepsilon$ 3900); NMR $\delta$: 1.11 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.28 (3H, s, 5-$CH_3$), 2.18 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.81, 3.54 (each 1H, d, $J$=18.5 Hz, 9-H), 3.0—3.4 (4H, m, $\overset{CH_2S}{\underset{CH_2S}{}}>$), 7.07 (1H, q, $J$=1 Hz, 12-H); MS $m/z$ (% rel. int.): 338 ($M^+$, 80), 245 (6), 132 (100).

b) From (±)-**3**: A mixture of (±)-**3** (17.7 mg), ethanedithiol (610 $\mu$l) and $BF_3$–$OEt_2$ (1 drop) in 2.5 ml of $CH_2Cl_2$ was stirred at room temperature overnight. The same work-up as described above afforded 19.4 mg (85%) of **24**.

**Desulfurization of 24 with Raney Nickel**——To a refluxing solution of **24** (203 mg) in 11 ml of EtOH was added Raney Ni (W-2; 5 g) and the reaction mixture was refluxed for 1 h. The nickel was filtered off and the filtrate was evaporated to dryness *in vacuo*. The products were separated by silica gel preparative TLC to afford 106 mg (71%) of (±)-**4** and 7 mg (5%) of the dehydro compound (**25**).

(±)-**4**: mp 120—121 °C, colorless prisms (recrystallized from AcOEt–hexane); High-resolution mass spectrum for $C_{15}H_{20}O_3$: Mol. Wt. 248.1411. Observed: $M^+$ 248.1421. IR $cm^{-1}$: 3475 (OH), 1670, 1650 (CO); UV $\lambda_{max}^{EtOH}$ 266 nm ($\varepsilon$ 3700); NMR $\delta$: 0.78 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.17 (3H, s, 5-$CH_3$), 2.20 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.74, 3.48 (each 1H, d, $J$=18 Hz, 9-H), 7.06 (1H, q, $J$=1 Hz, 12-H); MS $m/z$ (% rel. int.): 248 ($M^+$, 38), 179 (5), 166 (5), 122 (100).

The Dehydro Compound (**25**): Oil; High-resolution mass spectrum for $C_{15}H_{18}O_3$: Mol. Wt. 246.1251. Observed: $M^+$ 246.1264. IR $cm^{-1}$: 3460 (OH), 1675, 1645 (CO); NMR $\delta$: 0.89 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.12 (3H, s, 5-$CH_3$), 2.19 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.78, 3.32 (each 1H, d, $J$=18 Hz, 9-H), 5.4—5.6 (2H, m, 2, 3-H), 7.06 (1H, q, $J$=1 Hz, 12-H); MS $m/z$ (% rel. int.): 246 ($M^+$, 100), 213 (10), 178 (12), 122 (95).

**6-Epitetradimodiol (26)**——To a solution of (±)-**4** (30 mg) in 6 ml of dry ether was added 14 mg of $LiAlH_4$ and the mixture was stirred at room temperature for 2.5 h. Subsequent work-up as usual and purification over silica gel gave 22 mg (73%) of (±)-6-epitetradimodiol (**26**) as an unstable oil. High-resolution mass spectrum for $C_{15}H_{22}O_3$: Mol. Wt. 250.1567. Observed: $M^+$ 250.1559. IR $cm^{-1}$: 3450 (OH); NMR $\delta$: 1.03 (3H, d, $J$=6.5 Hz, 4-$CH_3$), 1.14 (3H, s, 5-

$CH_3$), 2.10 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.37, 3.23 (each 1H, d, $J$=18 Hz, 9-H), 4.89 (1H, br s, 6-H), 7.04 (1H, q, $J$=1 Hz, 12-H).

**3,3-Ethylenedioxy-6β-isobutyryloxy-$\Delta^{1,10}$-furanoeremophilan-6-one (27b)**——A solution of **27a** (134 mg), isobutyric anhydride (670 μl), and DMAP (67 mg) in 670 μl of pyridine was warmed at 50 °C for 4.5 h. Removal of the pyridine and isobutyric anhydride by evaporation *in vacuo* gave a yellow residue, which was purified by silica gel preparative TLC to give 154 mg (93%) of **27b**, as an oil. High-resolution mass spectrum for $C_{21}H_{26}O_6$: Mol. Wt. 374.1727. Observed: $M^+$ 374.1720. IR $cm^{-1}$ ($CHCl_3$): 1730, 1675 (CO), 1635 (C=C); UV $\lambda_{max}^{EtOH}$ 243.5, 300.5 nm; NMR δ: 1.02 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.27 (3H, s, 5-$CH_3$), 1.28, 1.30 (each 3H, d, $J$=7 Hz, isobutyl-$CH_3$), 1.91 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.72 (1H, quintet, $J$=7 Hz, isobutyl-H), 3.7—4.1 (4H, m, $\overset{CH_2O}{\underset{CH_2O}{>}}$), 6.63 (1H, dd, $J$=4, 5 Hz, 1-H), 6.86 (1H, s, 6-H), 7.37 (1H, q, $J$=1 Hz, 12-H); MS *m/z* (% rel. int.): 374 ($M^+$, 1.5), 100 (100).

**Catalytic Reduction of 27b**——Catalytic reduction of **27b** (110 mg) in 8 ml of AcOEt with 55 mg of Pd-C (10%) under an $H_2$ atmosphere was carried out at room temperature for 1 h. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was separated by column chromatography on silica gel to give **28a** (25 mg; 22%) and **28b** (80 mg; 72%).

3,3-Ethylenedioxy-6β-isobutyryloxy-10βH-furanoeremophilan-9-one (**28a**): mp 129.5—131 °C (from AcOEt–hexane), High-resolution mass spectrum for $C_{21}H_{28}O_6$: Mol. Wt. 376.1878. Observed: $M^+$ 376.1879. IR $cm^{-1}$: 1725, 1675 (CO); UV $\lambda_{max}^{EtOH}$ 284 nm (ε 14200); NMR δ: 0.90 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.14, 1.17 (each 3H, d, $J$=7.5 Hz, isobutyl-$CH_3$), 1.24 (3H, s, 5-$CH_3$), 2.02 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.56 (1H, quintet, $J$=7.5 Hz, isobutyl-H), 3.7—4.1 (4H, m, $\overset{CH_2O}{\underset{CH_2O}{>}}$), 6.14 (1H, br s, 6-H), 7.35 (1H, q, $J$=1 Hz, 12-H); MS *m/z* (% rel. int.): 376 ($M^+$, 3), 259 (7), 99 (100).

3,3-Ethylenedioxy-6β-isobutyryloxy-10αH-furanoeremophilan-9-one (**28b**): Oil, High-resolution mass spectrum for $C_{21}H_{28}O_6$: Mol. Wt. 376.1878. Observed: $M^+$ 376.1905. IR $cm^{-1}$: 1720, 1685 (CO); UV $\lambda_{max}^{EtOH}$ 277.5 nm; NMR δ: 0.89 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.08 (3H, s, 5-$CH_3$), 1.25 (6H, d, $J$=7 Hz, isobutyl-$CH_3$), 1.87 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.66 (1H, quintet, $J$=7 Hz, isobutyl-H), 3.7—4.1 (4H, m, $\overset{CH_2O}{\underset{CH_2O}{>}}$), 6.32 (1H, s, 6-H), 7.30 (1H, q, $J$=1 Hz, 12-H); MS *m/z* (% rel. int.): 376 ($M^+$, 15), 289 (17), 99 (100).

**Hydroxylation of 28 with Benzeneseleninic Anhydride**——A mixtutre of **28b** (64 mg), $(PhSeO)_2O$ (270 mg) and NaH (50% in mineral oil; 12 mg) in 3 ml of chlorobenzene was stirred under reflux for 1.5 h. The reaction mixture was cooled to room temperature and the resulting precipitate was filtered off. The filtrate was evaporated to dryness and the residue was separated by silica gel preparative TLC to give **29a** (30 mg; 45%) and **29b** (27 mg; 40%).

3,3-Ethylenedioxy-10β-hydroxy-6β-isobutyryloxyfuranoeremophilan-9-one (**29a**): mp 123.5—126 °C (colorless prisms from AcOEt–hexane), High-resolution mass spectrum for $C_{21}H_{28}O_7$: Mol. Wt. 392.1827. Observed: $M^+$ 392.1811. IR $cm^{-1}$: 3475 (OH), 1745, 1670 (CO); UV $\lambda_{max}^{EtOH}$ 282 nm (ε 15600); NMR δ: 1.10 (6H, br s, 4, 5-$CH_3$), 1.22, 1.24 (each 3H, d, $J$=7 Hz, isobutyl-$CH_3$), 1.93 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.65 (1H, quintet, $J$=7 Hz, isobutyl-H), 3.75—4.0 (4H, m, $\overset{CH_2O}{\underset{CH_2O}{>}}$), 7.42 (1H, q, $J$=1 Hz, 12-H); MS *m/z* (% rel. int.): 392 ($M^+$, 3), 304 (55), 99 (100).

3,3-Ethylenedioxy-10α-hydroxy-6β-isobutyryloxyfuranoeremophilan-9-one (**29b**): Oil, High-resolution mass spectrum for $C_{21}H_{28}O_7$: Mol. Wt. 392.1827. Observed: $M^+$ 392.1796. IR $cm^{-1}$: 3450 (OH), 1730, 1690 (CO); UV $\lambda_{max}^{EtOH}$ 282 nm; NMR δ: 0.85 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.12 (3H, s, 5-$CH_3$), 1.24 (6H, d, $J$=7 Hz, isobutyl-$CH_3$), 1.88 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.58 (1H, q, $J$=7 Hz, 4-H), 2.68 (1H, quintet, $J$=7 Hz, isobutyl-H), 3.7—4.1 (4H, m, $\overset{CH_2O}{\underset{CH_2O}{>}}$), 6.51 (1H, s, 6-H), 7.35 (1H, q, $J$=1 Hz, 12-H); MS *m/z* 392 ($M^+$).

**Acetal Exchanges of 29 to the Thioacetal 30**——a) A solution of **29a** (30 mg), ethanedithiol (550 μl) and $BF_3$–$OEt_2$ (4 drops) in 2.2 ml of $CH_2Cl_2$ was stirred at room temperature for 2 d. The reaction mixture was diluted with ether and washed with sat. aq. $NaHCO_3$ followed by sat. brine. The product was purified by column chromatography on silica gel to give 28 mg (87%) of **30a**, mp 185—187 °C (colorless prisms from AcOEt–hexane). High-resolution mass spectrum for $C_{21}H_{28}O_5S_2$: Mol. Wt. 424.1371. Observed: $M^+$ 424.1388. IR $cm^{-1}$: 3475 (OH), 1705, 1680 (CO); UV $\lambda_{max}^{EtOH}$ 285.5 nm (ε 14100); NMR δ: 1.15, 1.20 (each 3H, d, $J$=7 Hz, isobutyl-$CH_3$), 1.27 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.30 (3H, s, 5-$CH_3$), 2.02 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.58 (1H, quintet, $J$=7 Hz, isobutyl-H), 3.0—3.4 (4H, m, $\overset{CH_2S}{\underset{CH_2S}{>}}$), 6.26 (1H, br s, 6-H), 7.47 (1H, q, $J$=1 Hz, 12-H); MS *m/z* (% rel. int.): 424 ($M^+$, 1.5), 406 (1.7), 131 (100).

b) Treatment of **29b** (27 mg) with ethanedithiol (500 μl) and $BF_3$–$OEt_2$ (4 drops) in 2 ml of $CH_2Cl_2$ in the same manner as described above gave 24 mg (83%) of **30b**, mp 199—200 °C (colorless needles from AcOEt–hexane). High-resolution mass spectrum for $C_{21}H_{28}O_5S_2$: Mol. Wt. 424.1371. Observed: $M^+$ 424.1363. IR $cm^{-1}$: 3400 (OH), 1730, 1680 (CO); UV $\lambda_{max}^{EtOH}$ 282.5 nm (ε 14200); NMR δ: 1.11 (3H, s, 5-$CH_3$), 1.17 (3H, d, $J$=7 Hz, 4-$CH_3$), 1.24 (6H, d, $J$=7 Hz, isobutyl-$CH_3$), 1.87 (3H, d, $J$=1 Hz, 11-$CH_3$), 2.62 (1H, quintet, $J$=7 Hz, isobutyl-H), 3.0—3.4 (4H, m, $\overset{CH_2S}{\underset{CH_2S}{>}}$), 6.45 (1H, s, 6-H), 7.36 (1H, q, $J$=1 Hz, 12-H); MS *m/z* (% rel. int.): 424 ($M^+$, 1.2), 406 (1.2), 131 (100).

**10α-Hydroxy-6β-isobutyryloxyfuranoeremophilan-9-one (31)**——To a refluxing solution of **30b** (16 mg) in 1.2 ml of EtOH was added Raney Ni (W-2; 480 mg) and the reaction mixture was stirred and refluxed for 1 h. The nickel was filtered off and the filtrate was evaporated to dryness *in vacuo*. The product was purified by silica gel preparative TLC to afford 5.3 mg (42%) of **31**, mp 190—193 °C (colorless needles from AcOEt–hexane). High-resolution mass spectrum for $C_{19}H_{26}O_5$: Mol. Wt. 334.1773. Observed: 334.1804. IR $cm^{-1}$: 3450 (OH), 1720, 1680 (CO); UV $\lambda_{max}^{EtOH}$ 281.5 nm (ε 14200); NMR δ: 0.85 (3H, d, $J=7$ Hz, 4-$CH_3$), 0.96 (3H, s, 5-$CH_3$), 1.23 (6H, d, $J=7$ Hz, isobutyl-$CH_3$), 1.87 (3H, d, $J=1$ Hz, 11-$CH_3$), 2.62 (1H, quintet, $J=7$ Hz, isobutyl-H), 6.50 (1H, s, 6-H), 7.34 (1H, q, $J=1$ Hz, 12-H); MS *m/z* (% rel. int.): 334 ($M^+$, 0.5), 316 (15), 246 (100).

**(±)-10β-Hydroxy-6β-isobutyryloxyfuranoeremophilan-9-one (5)**——To a refluxing solution of **30a** (13 mg) in 2 ml of EtOH was added Raney Ni (W-2; 240 mg) and the reaction mixture was stirred and refluxed for 30 min. The same work-up as described above gave 4 mg (39%) of (±)-**5**, mp 153—157 °C (colorless prisms from AcOEt–hexane). High-resolution mass spectrum for $C_{19}H_{26}O_5$: Mol. Wt. 334.1773. Observed: $M^+$ 334.1786. IR $cm^{-1}$: 3475 (OH), 1700, 1680 (CO); UV $\lambda_{max}^{EtOH}$ 281 nm (ε 16100); NMR δ: 1.02 (3H, s, 5-$CH_3$), 1.09 (3H, d, $J=7$ Hz, 4-$CH_3$), 1.23, 1.26 (each 3H, d, $J=7$ Hz, isobutyl-$CH_3$), 1.96 (3H, d, $J=1$ Hz, 11-$CH_3$), 2.67 (1H, quintet, $J=7$ Hz, isobutyl-H), 6.58 (1H, br s, 6-H), 7.43 (1H, q, $J=1$ Hz, 12-H); MS *m/z* (% rel. int.): 334 ($M^+$, 2), 246 (41), 71 (67), 43 (100).

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