

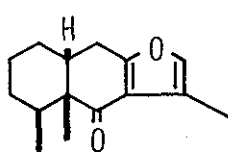
TOTAL SYNTHESIS OF (±)-FURANOEREMOPHILONE, (±)-9-HYDROXY-FURANOEREMOPHILANE, AND (±)-4-EPIFURANOEREMOPHILANES^{1,*}

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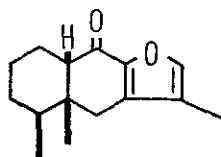
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Total syntheses of (±)-furanoeremophilone (2), (±)-9-hydroxyfuranoeremophilane (3), and (±)-4-epifuranoeremophilanes starting from the diene adduct (4) are described.

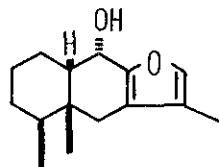
In a previous paper,² we reported the total synthesis of sesquiterpene (±)-ligularone (1) starting from the diene adduct (4) of 3-ethoxy-1,3-pentadiene and dimethylfuranobenzquinone. In this communication, we report the total syntheses of (±)-furanoeremophilone (2),³ (±)-9-hydroxyfuranoeremophilane (3),⁴ and (±)-4-epifuranoeremophilane (12) starting from the diene adduct (4).



(1)



(2)

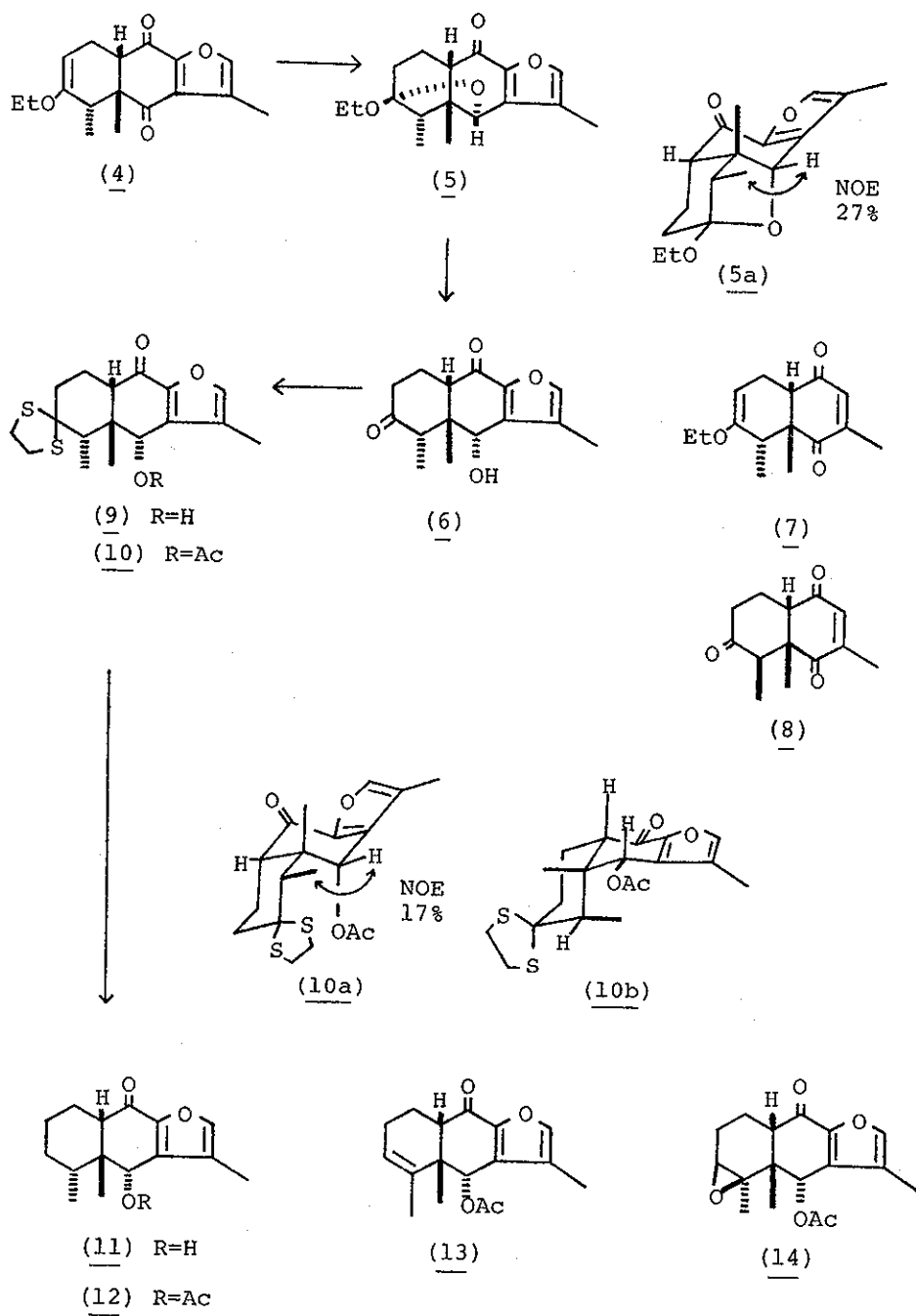


(3)

* Dedicated to Professor Sugasawa on the Anniversary of His 80th Birthday.

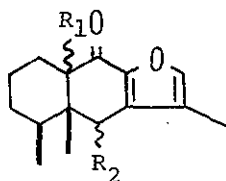
Reduction of the diene adduct (4) with excess NaBH_4 in the presence of NH_4Cl , followed by treatment with silica gel afforded an ether (5), mp $128-130^\circ$ [MS: m/e 290, M^+], in a quantitative yield. The stereoformula of (5) was determined as a cyclic non-steroidal form (5a) from its spectral data. A carbonyl and ether absorption bands appeared at 1693 and 1110 cm^{-1} , respectively, in IR spectrum of (5), and an absorption maxima at 237 and 283 nm for a α -acylsubstituted furan chromophor in its UV spectrum. The NMR spectrum of (5) showed a singlet signal at δ 4.84 for C-6 proton. The stereochemistry of (5a) was confirmed by nuclear Overhauser effect (NOE) measurements in carefully degassed CDCl_3 solution of (5).⁵ Irradiation of 4-methyl group signals centered at δ 1.11 (d, $J=7\text{ Hz}$) resulted in a 27% enhancement of the 6-H β signal. From these facts, conformation of the ether (5) must show a non-steroidal chair-chair form (5a).

Hydrolysis of the ether (5) with aqueous AcOH gave a ketol (6), mp $199-206^\circ$, quantitatively. IR spectrum of (6) showed two carbonyl absorption bands at 1696 and 1682 cm^{-1} , and an absorption band at 3425 cm^{-1} for a hydroxyl group. Schmidt *et al.*⁶ reported that C-4 α methyl group of octalin derivative (7) epimerized to C-4 β methyl derivative (8), but the C-4 α methyl group of (6) did not epimerize under the same conditions. Treatment of (6) with ethanedithiol in ether in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ complex gave a dithio-ketal (9), mp $245-248^\circ$, in 53% yield. The thioketal (9) was warmed in Ac_2O -pyridine at 100° for 22 hr to afford an acetate (10), mp $183-184.5^\circ$, in 60% yield. (10) may possibly exist in two forms, a non-steroidal form (10a) and a steroidal form (10b). The NOE



value of 17% enhancement is observed for C-6 β proton signal, on irradiation of C-4 methyl group signals (δ 1.37). This NOE result supported a non-steroidal form (10a) for the conformation of this ketal (10).

Attempted desulfurization of the thioketal (9) with Raney nickel catalyst in EtOH for conversion to (11) was unsuccessful. Reductive desulfurization of (10) with Raney nickel catalyst in EtOH was carried out with refluxing for 15 min gave a mixture of ketol acetate (12) and a dehydro compound (13) in 3:1 ratio. Separation and catalytic hydrogenation of the mixture of (12) and (13) were unsuccessful. Treatment of the mixture with *m*-chloroperbenzoic acid in CH₂Cl₂ and followed by separation gave pure (12), mp 151-152°, and an epoxide (14), mp 225-226°. The NMR data of (12) did not agree with those of the natural four isomeric ketol acetates (15a-d) derived from isoadenostylone (16) and decompostin (17) reported by Novotny *et al.*³ Therefore, the structure of (12) was confirmed to be (\pm)-4-*epi*-6-acetoxymorphoeremophil-9-one.

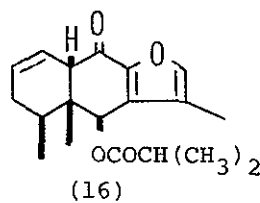


(15a) R₁= β -H R₂= β -OAc

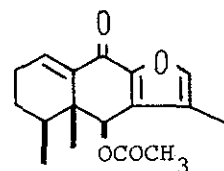
(15b) R₁= β -H R₂= α -OAc

(15c) R₁= α -H R₂= β -OAc

(15d) R₁= α -H R₂= α -OAc



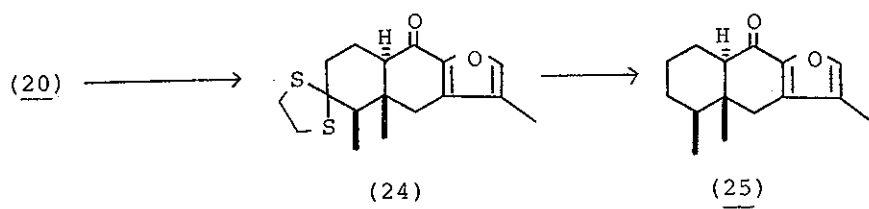
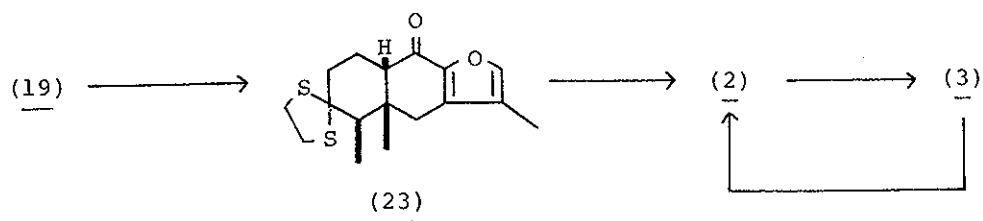
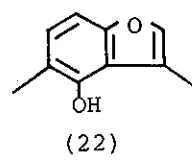
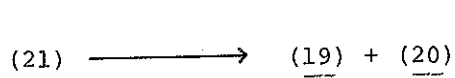
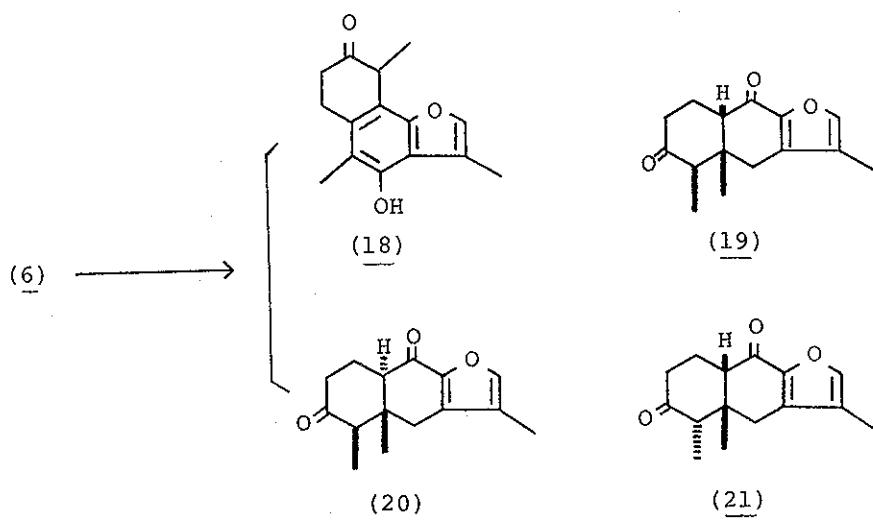
(16)



(17)

Next, we attempted total synthesis of (\pm)-furanoeremophilone (2) and related natural products. Treatment of the diketo-ol (6) with red phosphorus and iodine in AcOH afforded a mixture of compounds, which were separated by chromatographic procedure to give a benzofuran derivative (18; 9-10% yield), mp 185-189°, and diketones (19; 20% yield), mp 166-170°, (20; 28-30% yield), mp 199-202°, and (21; 30% yield), as an oil. The structure of benzofuran derivative (18) was presumed from its spectral data. Its UV spectrum pattern was very similar to that of 3,5-dimethyl-4-hydroxybenzofuran (22)² and NMR spectrum of (18) showed three methyl signals at δ 2.47 (s), 2.37 (d, $J=1$ Hz), and 1.37 (d, $J=7$ Hz). The diketones (19-21) showed the same molecular ion peak at m/e 246 in their mass spectra. IR, UV, and NMR data of the diketones (19 and 20) were in good agreement with those of authentic samples reported by Takahashi *et al.*⁷ and Rivett *et al.*⁸ Consequently, structure of the diketones, (19 and 20), was confirmed as 10 β (H)- and 10 α (H)-furanoeremophil-3,9-dione, respectively. Structure of the diketone (21), an oily product, was found to be 4-*epi*-10 β (H)-furanoeremophil-3,9-dione [IR: 1715, 1680 cm^{-1} ; UV $\lambda_{\text{max}}^{\text{EtOH}}$ 281 nm; NMR δ : 1.09 (3H, d, $J=7$ Hz), 1.20 (3H, s), 1.96 (3H, d, $J=1$ Hz), 7.40 (1H, m)]. Treatment of (21) with *p*-toluenesulfonic acid in refluxing benzene for 2 hr gave (19), (20), and (21) in 23%, 18%, and 41% yield, respectively.

Treatment of the diketones (19 and 20) with ethanedithiol in ether in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ complex at room temperature for 4 days gave the corresponding 3-thioketal derivatives (23), mp 177-179°, and (24), mp 202-205°, in 74% and 59% yield, respectively.



Reductive desulfurization of (23) and (24) with Raney nickel catalyst in refluxing EtOH for 15 min gave the ketones, (2), mp 130.5-132°, and (25), mp 109-111°, in 84% and 82% yield, respectively. [2; IR cm^{-1} : 1661 (CO), 1534 (furan); UV $\lambda_{\text{max}}^{\text{EtOH}}$ 281 nm (ϵ 14800); NMR δ : 0.88 (3H, d, $J=7$ Hz, 4-Me), 1.06 (3H, s, 5-Me), 1.97 (3H, d, $J=1$ Hz, 11-Me), 2.24 and 2.95 (1H each, d, $J=17$ Hz, 6- H_2), 7.35 (1H, m, 12-H)] [25; IR cm^{-1} : 1656 (CO), 1530 (furan); UV $\lambda_{\text{max}}^{\text{EtOH}}$ 279 nm (ϵ 15600); NMR δ : 0.78 (3H, s, 5-Me), 0.93 (3H, d, $J=7$ Hz, 4-Me), 1.98 (3H, d, $J=1$ Hz, 11-Me), 2.43 and 2.70 (1H each, d, $J=16$ Hz, 6- H_2), 7.32 (1H, m, 12-H)]. IR, UV, and NMR spectral data of the ketones (2 and 25) agreed well with those of natural *cis*- and *trans*-annulated furanoeremophilone isolated from the light petroleum extract of *Petasites hybridus* (L.) rhizomes by Novotny *et al.*^{3,4}, respectively.

Reduction of (\pm)-(2) with LiAlH_4 in ether at 0°C for 1 hr gave (\pm)-9 α -hydroxyfuranoeremophilane⁴ (3), an oily product, in 85% yield [MS: m/e 234, M^+ ; IR 3420 cm^{-1} (OH); NMR δ : 0.88 (s, 5-Me), 1.03 (d, $J=7$ Hz, 4-Me), 1.89 (d, $J=1$ Hz, 11-Me), 2.80 (bd, $J=16$ Hz, 6- H_2), 4.81 (bd, $J=5$ Hz, 9 β -H), 7.12 (m, 13-H)]. Oxidation of (3) with activated MnO_2 in benzene at room temperature for 1.5 hr gave (2) in 80% yield, which showed identical NMR spectrum and GLC as that of authentic (\pm)-furanoeremophilone.

REFERENCES AND NOTES

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- 9 Added in Proof - The NMR spectrum of (\pm) -3 was not identical with that of natural 9-hydroxyfuranoeremophilane isolated from *P. hybridus* (L.).⁴ Dr. Novotny, Czechoslovak Academy of Science, has kindly informed us that the correct structure of natural 9-hydroxy derivative should be shown 9 β -hydroxy compound (26).

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