D:A Friedo-oleanane Lactones from the Stems of *Mallotus repandus*[⊥]

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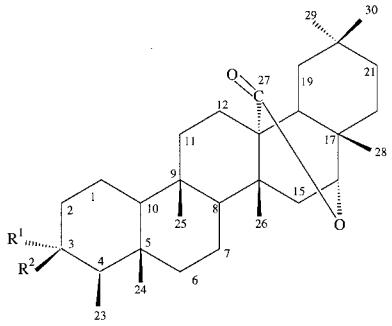
Three new D:A-friedo-oleanane lactones, viz., 3-oxo-D:A-friedo-oleanan-27,16α-lactone (**1**), 3α-benzoyloxy-D:A-friedo-oleanan-27,16α-lactone (**2**), and 3*β*-hydroxy-D:A-friedo-oleanan-27,16α-lactone (**3**) were isolated from the stems of *Mallotus repandus*. Extensive use of NMR spectroscopic techniques led to full assignment of all ^{1}H and ^{13}C chemical shifts. The structure for **2** was confirmed by X-ray diffraction analysis.

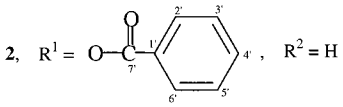
Mallotus repandus (Willd.) Mueller-Arg. (Euphorbiaceae) is a creeping shrub commonly known as "Ma Kaai Khruea" in Thailand.[1] The aerial part has been used as an anti-inflammatory, antigastric ulcer, antiulcerogenic, and anti-hepatotoxic drug. Dry roots have been used as an insecticide and as a treatment for rheumatic arthritis, hepatitis, liver cirrhosis, and snakebite. Previous studies of this plant yielded bergenin,[2] diterpenic lactones,[3] *δ*-lactone triterpenes,[4,5] mallorepine, a cyano-*γ*-pyridone,[6] and hydrolyzable tannins.[7] We report here the isolation and structure elucidation of three new D:A-friedo-oleanane lactones. Structures were supported by an X-ray analysis of **2**. This is the first report of the occurrence of D:A-friedo-oleanane lactones in Euphorbiaceae plants.

Results and Discussion

The hexane extract of dried stems of *M. repandus* was subjected to repeated column chromatography to give three D:A-friedo-oleanane lactones (**1**−**3**). Identification of pure compounds was based on spectroscopic data.



1, $R^1 = R^2 = O$



2, R^1 = , R^2 = H

3, R^1 = H, R^2 = OH

Compound **1**, mp 350 °C, gave a violet coloration upon treatment with anisaldehyde-sulfuric acid staining reagent on a TLC plate after heating. The EIMS gave a molecular ion at *m*/*z* 454 corresponding to the molecular formula $C_{30}H_{46}O_3$. The IR spectrum indicated the presence of a six-membered or larger ring lactone (C=O stretching at ν_{max} 1730 cm^{-1}, C−O stretching at 1118 cm^{-1}) and showed C=O stretching of a saturated ketone at 1714 cm^{-1}. The ^{1}H NMR spectrum showed six methyl group singlets and one methyl group doublet. The ^{13}C NMR spectrum showed the presence of 30 carbons consisting of seven methyl, 10 methylene, five methine, and six quaternary carbons together with two carbonyl signals at δ_C 177.0 and 212.0. The 3-oxo friedelane skeleton was implied by the presence of a shielded methyl group signal at δ_C 6.8, which was found to have a one-bond correlation with the methyl proton doublet at δ_H 0.85 by a HETCOR experiment.[8] Multiplets between δ_H 2.29−2.36 and a quartet at δ_H 2.20 (J = 6.8 Hz) were assigned to the C-2 methylene and C-4 methine protons, respectively. The presence of a signal at δ_H 3.98 (dd, J = 2.1, 3.2 Hz) indicating an oxymethine proton on a carbon bonded to an −OCO−R group, together with the ^{13}C signal at δ_C 177.0 corresponding to a carbonyl carbon, indicated a lactone moiety.

Friedelane-type triterpenes are proposed to have rings D and E in a boat−boat conformation.[9] This being the case, it could clearly be envisaged using molecular models that the six-membered lactone ring can only be formed favorably as a 27,16-α-lactone ring. The dihedral angle between protons H-15 and H-16 is about 60°, thus giving rise to the small ^3J coupling constants observed. Compound **1** was therefore proposed to be 3-oxo-D:A-friedo-oleanan-27,16α-lactone. Extensive use of NMR techniques including ^{1}H−^{1}H COSY, ^{13}C−^{1}H COSY (HETCOR), and long-range ^{13}C−^{1}H correlation (COLOC) (Figure 1, Supporting Information) led to complete assignments of all ^{1}H and ^{13}C shift values as indicated in the Experimental Section.

Compound **2**, mp 340−342 °C, gave a violet coloration upon treatment with anisaldehyde-sulfuric acid reagent and a dark blue color in response to phosphomolybdic acid. The EIMS showed a molecular ion at *m*/*z* 560 corresponding to the molecular formula $C_{37}H_{52}O_4$. The IR spectrum showed absorption bands at ν_{max} 1731 and 1712 cm^{-1} for C=O stretching of a large-ring lactone and an aryl ester, respectively. The ^{1}H NMR spectrum showed a pattern of signals similar to that found for compound **1**, except for the absence of multiplets between δ_H 2.20−2.36, which had been assigned as C-2 methylene and C-4 methine protons

[⊥] In honor of Professor Wolfgang Kraus upon his retirement.

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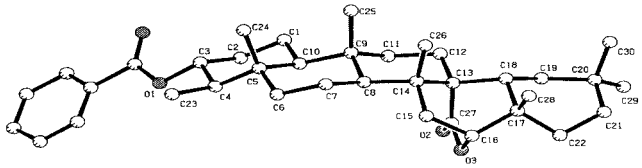

Figure 1. ORTEP structure of **2**.

bonded to a C-3 carbonyl carbon. The presence of a signal at δ_H 4.87 due to a single proton, together with a double triplet of two protons at δ_H 7.44, a one-proton double triplet at δ_H 7.55, and a two-proton doublet of doublets at δ_H 8.03 required a β-oriented proton bonded to an O-benzoylated C-3 atom. The stereochemistry of the compound was obtained from the NOESY experiment (Figure 2, Supporting Information). The key interactions between H-3/H-2e, H-3/C-24-H, and H-3/H-1a indicated the C-3 proton to be axial. Compound **2** was concluded to be 3α-benzoyloxy-D:A-friedo-oleanan-27,16α-lactone. An X-ray crystal structure determination of **2** confirmed the relative stereochemistry (Figure 1). The ^{1}H and ^{13}C NMR shifts were assigned as indicated in the Experimental Section. The 3β-epimer of this compound, 3β-benzoyloxy-D:A-friedo-oleanan-27,16α-lactone, was recently isolated from *Homalium longifolium*.[10]

Compound **3**, mp 338−340 °C, gave a purple color with anisaldehyde-sulfuric acid reagent on a TLC plate upon heating. The EIMS gave a molecular ion at *m/z* 456 corresponding to the molecular formula $C_{30}H_{48}O_3$. The IR spectrum showed OH stretching at ν_{max} 3470 cm^{-1} together with bands at 1727 and 1116 cm^{-1}, which were characteristic for a six-membered ring lactone. The ^{1}H NMR spectrum revealed a pattern of signals similar to that found for compounds **1** and **2**. A broad singlet at δ_H 3.72 (width at half-peak height = 7.7 Hz) corresponded to the oxymethine proton bonded to the oxygenated carbon at C-3. The small ^3J-coupling of C-3-H with the C-2 and C-4 protons, which resulted in an unresolved multiplet, indicated an α-oriented C-3 proton. Compound **3** was concluded to be 3β-hydroxy-D:A-friedo-oleanan-27,16α-lactone. Cross-correlations between H-3/C-23-H and H-3/H-4 from the NOESY spectrum (Figure 2, Supporting Information) gave support to the proposed structure. The ^{1}H and ^{13}C chemical shifts were assigned as indicated in the Experimental Section.

Experimental Section

General Experimental Procedures. Melting points are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. The magnitude of the delay for optimizing one-bond correlations was 3.45 ms, and the evolution delay for long-range coupling (COLOC) was set to 25 ms (J = 20 Hz). Optical rotations were obtained with a Jasco model DIP-370 digital polarimeter, IR spectra were recorded on a Jasco IR-700 spectrophotometer, and EIMS were determined on a Finnigan MAT 8200 mass spectrometer.

Plant Material. The stems of *Mallotus repandus* (Willd.) Mueller-Arg (Euphorbiaceae) were collected from Kao Hin Son in Chachuansao Province (southeast of Bangkok) during the summer of 1995. The plant was identified by comparison with the herbarium specimen kept at the Forest Herbarium, Royal Forest Department, Bangkok (BKF. No. 31325). A voucher specimen (SSMR/1995) is kept at the Department of Chemistry, Faculty of Science, Ramkhamhaeng University.

Extraction and Isolation. The dried stems of *M. repandus* were milled to obtain 6 kg of powder, which was extracted successively with *n*-hexane, $CHCl_3$, and MeOH in a Soxhlet extractor. After evaporation of the solvents under reduced pressure, the hexane (27.75 g), $CHCl_3$ (20.41 g), and MeOH (61 g) extracts were obtained.

The hexane extract was subjected to a silica gel column chromatography eluting with a gradient of hexane−$CHCl_3$ (10:0 to 0:10) followed by $CHCl_3$−MeOH (10:0 to 1:1). Seventy 250 mL fractions were collected, monitored by TLC, and combined to yield four major fractions. Fraction 1 was subjected to additional column chromatography (silica gel, hexane−$CHCl_3$, 10:1) to yield a mixture of long-chain fatty acid esters consisting mainly of tetracosyl tetracosanoate (21.6 mg, 0.00036 w/w%) after recrystallization (MeOH−$CHCl_3$). Fraction 2 was subjected to additional silica gel column chromatography (2×, hexane−$CHCl_3$, 1:1) to obtain 3α-benzoyloxy-D:A-friedo-oleanan-27,16α-lactone (**2**) (207 mg, 0.00345 w/w%). Fraction 3 was purified further by silica gel column chromatography (hexane−$CHCl_3$, 1:1) to obtain three subfractions. Subfraction 1 was subjected to column chromatography (silica gel, hexane−$CHCl_3$, 3:7) to obtain crystalline 3α-benzoyloxy-D:A-friedo-oleanan-27,16α-lactone (**2**) (185 mg, 0.00308 w/w%). Subfraction 2 was subjected to chromatography (silica gel column, hexane−$CHCl_3$ 3:2) to obtain a mixture of stigmast-4-en-3-one and stigmast-4,11-dien-3-one (37.8 mg, 0.00063 w/w%) after recrystallization from MeOH; subfraction 3, after silica gel column chromatography (hexane−$CHCl_3$, 1:1), gave β-sitosterol (55.8 mg, 0.00093 w/w%) and 3β-hydroxy-D:A-friedo-oleanan-27,16α-lactone (**3**) (18 mg, 0.0003 w/w%). Fraction 4 was purified by silica gel column chromatography (2×, using $CHCl_3$ and hexane−$CHCl_3$, 1:9) to yield 3-oxo-D:A-friedo-oleanan-27,16α-lactone (**1**) (14.7 mg, 0.00024 w/w%).

The chloroform extract was chromatographed on a silica gel column with a gradient of $CHCl_3$−MeOH to give an additional quantity of **2** (150 mg, 0.0025 w/w%), β-sitosteryl-D-glucopyranoside (44.7 mg, 0.00074 w/w%)[11] and mallorepine (10 mg, 0.00016 w/w%).[6] Chromatographic separation of the methanol extract using a silica gel column and a gradient of $CHCl_3$−MeOH gave bergenin (2.5 g, 0.0417 w/w%)[2] and 3-*O*-methylellagic acid (5 mg, 0.0008 w/w%).[12] The known compounds were identified by comparison of MS, ^{1}H and ^{13}C NMR, and physical data with those reported previously.

3-Oxo-D:A-friedo-oleanan-27,16α-lactone (1): colorless needles, mp 350 °C (MeOH−$CHCl_3$); $[\alpha]_D^{27}$ −44.9° (*c* 1.165, $CHCl_3$); IR (KBr) ν_{max} 2946, 2864, 1730, 1714, 1454, 1389, 1352, 1118, 1000, 978 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.98 (1H, dd, J = 2.1, 3.2 Hz, H-16), 2.36 (1H, m, H-2a), 2.29 (1H, m, H-2b), 2.20 (1H, q, J = 6.8 Hz, H-4), 1.97 (2H, m, H-7a and H-18), 1.96 (1H, m, H-1a), 1.92 (1H, m, H-7b), 1.85 (2H, m, H-15), 1.73 (1H, m, H-6a), 1.65 (1H, m, H-1b), 1.58 (2H, m, H-11), 1.52 (1H, m, H-10), 1.49 (2H, m, H-12), 1.40 (2H, m, H-19), 1.24 (1H, m, H-6b), 1.20 (3H, s, H-28), 1.19 (3H, s, H-26), 1.10 (2H, m, H-21), 0.98 (3H, s, H-30), 0.95 (1H, m, H-8), 0.92 (3H, s, H-29), 0.89 (2H, m, H-22), 0.88 (3H, s, H-25), 0.85 (3H, d, J = 6.7 Hz, H-23), 0.71 (3H, s, H-24); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.0 (s, C-3), 177.0 (s, C-27), 83.5 (d, C-16), 58.4 (d, C-10), 57.8 (d, C-4), 57.5 (d, C-8), 51.4 (s, C-13), 42.1 (s, C-9), 41.3 (t, C-2), 40.4 (t, C-6), 39.5 (t, C-15), 39.0 (d, C-18), 38.0 (s, C-5), 37.6 (s, C-14), 36.5 (t, C-21), 36.1 (t, C-11), 35.9 (s, C-17), 34.6 (q, C-29), 31.4 (t, C-19), 30.5 (q, C-30), 30.0 (t, C-22), 27.9 (s, C-20), 23.3 (q, C-28), 22.2 (t, C-1), 21.5 (t, C-7), 20.4 (q, C-26), 18.9 (t, C-12), 17.8 (q, C-25), 14.5 (q, C-24), 6.8 (q, C-23); EIMS 70 eV *m/z* 454 $[M]^+$ (41), 436 (55), 423 (18), 407 (6), 383 (95), 370 (29), 355 (14), 315 (20), 314 (37), 269 (35), 255 (26), 219 (9), 187 (34), 175 (18), 133 (32), 107 (41), 95 (63), 54 (92); HR-EIMS *m/z* 454.3471 (calcd for $C_{30}H_{46}O_3$, 454.3447).

3α-Benzoyloxy-D:A-friedo-oleanan-27,16α -lactone (2): colorless needles, mp 340−342 °C (MeOH−$CHCl_3$; $[\alpha]_D^{27}$ −27.3° (*c* 0.33, $CHCl_3$); IR (KBr) ν_{max} 2942, 2866, 1731, 1712, 1600, 1450, 1388, 1360, 1313, 1271, 1171, 1111, 1067, 1044, 1026, 813, 709 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (2H, d, J = 7.1, 1.4 Hz, H-2′ and H-6′), 7.55 (1H, dt, J = 7.4, 1.8 Hz, H-4′), 7.44 (2H, dt, J = 7.6, 1.6 Hz, H-3′ and H-5′), 4.87 (1H, ddd, J = 10.7, 10.7, 5.1 Hz, H-3), 3.98 (1H, dd, J = 3.2, 2.3 Hz, H-16), 2.19 (2H, m, H-2), 1.97 (1H, m, H-18), 1.93 (2H, m, H-1), 1.85 (2H, m, H-15), 1.80 (2H, m, H-6), 1.67 (2H, m, H-12), 1.55 (2H, m, H-11), 1.48 (2H, m, H-7), 1.44 (1H, m, H-4), 1.41 (2H, m, H-19), 1.20 (3H, s, H-28), 1.19 (3H, s, H-26), 1.17

(2H, m, H-21), 1.02 (1H, m, H-10), 0.98 (3H, s, H-30), 0.93 (3H, s, H-29), 0.89 (2H, m, H-22), 0.87 (3H, s, H-24), 0.86 (3H, s, H-25), 0.86 (1H, m, H-8), 0.81 (3H, d, J = 6.7 Hz, H-23); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.0 (s, C-27), 166.4 (s, C-7′), 132.6 (d, C-4′), 130.9 (s, C-1′), 129.5 (d, C-2′ and C-6′), 128.3 (d, C-3′ and C-5′), 83.5 (d, C-16), 75.6 (d, C-3), 58.8 (d, C-10), 57.5 (d, C-8), 51.4 (s, C-13), 49.8 (d, C-4), 40.5 (t, C-6), 39.4 (t, C-15), 39.0 (d, C-18), 38.5 (s, C-5), 38.0 (s, C-14), 37.2 (s, C-9), 36.5 (t, C-21), 36.1 (t, C-11), 35.9 (s, C-17), 34.6 (q, C-29), 32.4 (t, C-2), 31.5 (t, C-19), 30.5 (q, C-30), 30.0 (t, C-22), 27.9 (s, C-20), 23.3 (q, C-28), 21.6 (t, C-1), 20.4 (q, C-26), 19.3 (t, C-12), 18.5 (t, C-7), 18.0 (q, C-25), 14.3 (q, C-24), 10.0 (q, C-23); EIMS 70 eV m/z 560 $[M]^+$ (2.4), 455 (1), 438 (37), 423 (22), 370 (32), 355 (9), 314 (51), 269 (20), 255 (16), 187 (19), 147 (13), 122 (13), 105 (100), 54 (45), 28 (15); HR-EIMS m/z 560.3916 (calcd for $C_{37}H_{52}O_4$, 560.3865).

X-ray Structure Analysis of 2. Suitable single crystals were obtained by slow evaporation of $CHCl_3$−hexanes−ethyl acetate solutions. A colorless crystal measuring 0.15 × 0.30 × 0.50 mm was mounted on an Enraf-Nonius MACH3 diffractometer with Mo Kα radiation (λ = 0.71073 Å) using a graphite monochromator. The final unit-cell parameters for a monoclinic crystal of molecular formula $C_{37}H_{52}O_4$, MW 560.79, Z = 4, calculated density = 1.22 g/cm^{-3}, were obtained by least-squares on the setting angle for 25 reflections as a = 6.388(1) Å, b = 35.655(5) Å, c = 13.381(1) Å, β = 91.96(1)°, V = 3045.7-(6) Å^3, with two independent molecules in the asymmetric unit and $F(000)$ = 1224e$^-$. The crystal data were collected at 298-(2) K in the ω−2θ scan mode using a variable scan speed in the 2−25° range to obtain 6231 reflections, of which 5475 reflections were unique and 2754 were considered as observed [$I \geq 2\sigma(I)$]. No crystal decay was observed, and the absorption coefficient μ = 0.077 mm^{-1} precluded the need of absorption corrections. The systematic absences of the observed reflections were consistent with the $P2_1$ space group. The structure was solved by direct methods using the SHELXS97 software. All non-hydrogen atoms were refined anisotropically in a full-matrix least-squares refinement process using SHELXL97 and converged to a final R-factor of 0.0856 (R_w = 0.1782 for 2754 observed data) with the goodness-of-fit of 1.057. A final difference Fourier map showed residual density between 0.358 and −0.365 e Å^{-3}. Atomic coordinates, bond lengths, bond angles, and thermal parameters have been deposited with the Cambridge Crystallographic Data Center (CCDC 149897). Copies of the data can be obtained free of charge on application to the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-(0) 1223−336033 or e-mail: deposit@ccdc.cam.ac.uk).

3β-Hydroxy-D:A-friedo-oleanan-27,16α-lactone (3): colorless needles, mp 338−340 °C (MeOH−$CHCl_3$); $[\alpha]_D^{27}$ −16.0° (c 0.1, $CHCl_3$); IR (KBr) ν_{max} 3470, 2940, 2866, 1727, 1448, 1355, 1351, 1116, 1045, 1000 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.97 (1H, dd, J = 3.5, 2.1 Hz, H-16), 3.72 (1H, br s, $W_{1/2}$ = 7.7 Hz, H-3), 1.95 (1H, m, H-18), 1.94 (1H, m, H-1a), 1.89 (1H, m, H-1b), 1.82 (4H, m, H-2 and H-15), 1.70 (2H, m, H-6), 1.58 (2H, m, H-11), 1.54 (2H, m, H-7), 1.41 (2H, m, H-19), 1.38 (2H, m, H-12), 1.22 (1H, m, H-4), 1.19 (3H, s, H-28), 1.17 (3H, s, H-26), 0.99 (2H, m, H-21), 0.98 (3H,s, H-30), 0.96 (3H,s, H-24), 0.91 (3H, d, J = 7.1 Hz, H-23), 0.89 (1H, m, H-10), 0.87 (2H, m, H-22), 0.87 (3H, s, H-25), 0.83 (1H, dd, J = 11.7, 1.96 Hz, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.0 (s, C-27), 83.5 (d, C-16), 72.5 (d, C-3), 60.1 (d, C-10), 57.6 (d, C-8), 51.4 (s, C-13), 48.7 (d, C-4), 40.8 (t, C-6), 39.4 (t, C-15), 39.0 (d, C-18), 38.1 (s, C-5), 37.8 (s, C-14), 37.2 (s, C-9), 36.5 (t, C-21), 36.1 (t, C-11), 35.9 (s, C-17), 34.9 (t, C-2), 34.6 (q, C-29), 31.5 (t, C-19), 30.5 (q, C-30), 30.0 (t, C-22), 27.9 (s, C-20), 23.3 (q, C-28), 21.6 (t, C-1), 20.3 (q, C-26), 18.1 (t, C-12), 18.1 (q, C-25), 16.2 (q, C-24), 15.7 (t, C-7), 11.6 (q, C-23); EIMS 70 eV m/z 456 $[M]^+$ (19), 438 (15), 385 (36), 370 (62), 314 (47), 269 (27), 256 (22), 249 (11), 187 (29), 165 (36), 94 (61), 55 (100); HR-EIMS m/z 456.3644 (calcd for $C_{30}H_{48}O_3$, 456.3603).

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Supporting Information Available: 2D NMR connectivity diagrams, COLOC for **1** and NOESY for **2** and **3**. This information is available free of charge via the Internet at http://pubs.acs.org.

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