Synthesis of 16,18-Dihydroxycleroda-3,13*Z*-dien-16,15-olide, (+)-16-Hydroxycleroda-3,13*Z*-dien-16,15-olide, and (−)-Hydroxyhalima-5(10),13-dien-16,15-olide from (+)-Hardwickiic Acid

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Syntheses of three enantiomers of natural hydroxybutenolide diterpenes, 16,18-dihydroxycleroda-3,13*Z*-dien-16,15-olide (**4**), (+)-16-hydroxycleroda-3,13*Z*-dien-16,15-olide (**5**), and (−)-16-hydroxyhalima-5(10),-13*Z*-dien-16,15-olide (**6**), via a furan photosensitized oxygenation reaction of (+)-hardwickiic acid (**2**), are described.

The occurrence of natural clerodane hydroxybutenolides such as **1** (Figure 1) has been reported frequently in plants of the genera *Polyalthia*,[2−11] *Acritopappus*,[12] *Premna*,[13] and *Cyathocalyx*.[14] It is interesting to note that many species of these genera are widely used in folk medicine as diuretics,[15] febrifuges,[4] and chewing sticks, and for sterilizing milk containers.[13] It is also noteworthy that some natural clerodane hydroxybutenolides show significant biological activities as antifeedants[2] and antimicrobials,[6,13] cytotoxicity to tumor cell cultures,[3,10] and toxicity against *Artemia salina*[3,14] and *Aedes aegypti*.[14] Recently, we described the isolation of two clerodane hydroxybutenolides from *Echinodorus grandiflorus* [Cham. & Schltdl.] Micheli (*Alismataceae*) and the synthesis of an enantiomer of one of them from (+)-hardwickiic acid (**2a**).[15] Although there are many reports in the literature for the synthesis of clerodane diterpenoids, only a few report the synthesis of clerodane hydroxybutenolides such as **1**[16,17] and **3**.[15] Thus, in connection with our studies regarding the use of resin acids as chiral starting materials for the synthesis of natural products,[18−20] and in view of the potential biological activities of natural hydroxybutenolides, we have synthesized clerodanes **4** and **5** and halimane **6**, with absolute configurations enantiomeric[21] to those of the natural products, from the readily available methyl (+)-hardwickiate (**2b**),[15,22] in order to facilitate comparisons of biological activities.

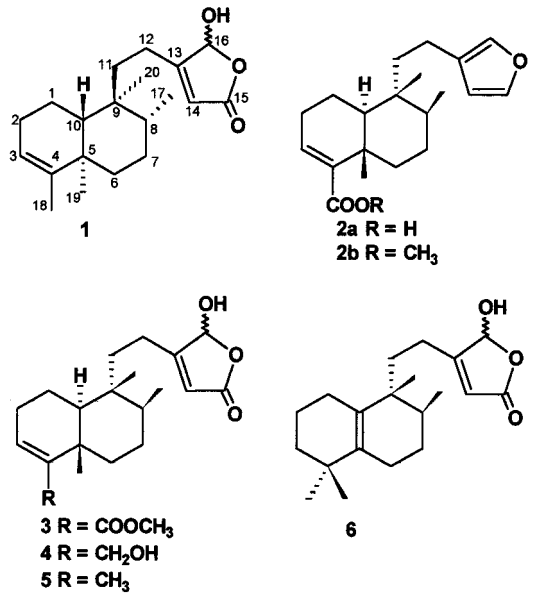
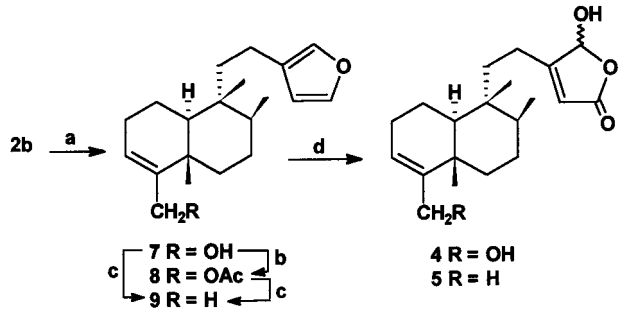


Figure 1.

Results and Discussion

Reduction of (+)-methyl hardwickiate (**2b**) with lithium aluminum hydride furnished a mixture (3:1) of the desired compound **7** and the corresponding Δ^3-dihydro compound, which are difficult to separate. However, reduction of **2b** with diisobutylaluminum hydride (DIBAL) furnished the desired alcohol **7** in 98% yield (Scheme 1). The next step for the synthesis of the hydroxybutenolide moiety from the furan ring was based on a photosensitized oxygenation procedure reported by Kernan and Faulkner.[23] Thus, reaction of **7** in CH_2Cl_2 at −78 °C with oxygen in the presence of Rose Bengal and diisopropylethylamine (DIPEA) furnished **4**, a diastereoisomer of a compound reported by Faulkner,[23] in 75% yield.

Scheme 1[a]



[a] Key: (a) DIBAL, toluene, −78 °C (98%); (b) Ac_2O, Py, rt, (85%); (**c**) nickel-boride, diglyme, 0 °C (73% from **7** and 75% from **8**); (d) O_2, Rose Bengal, DIPEA, CH_2Cl_2, −78 °C, (75% for **4** and 72% for **5**).

Reductive elimination of the hydroxyl group in **7** to yield **9** proved troublesome. Treatment of **7** with methanesulfonyl chloride led to a complex mixture of products, among which the desired mesylate and the corresponding chlorinated compound were tentatively identified. To circumvent this problem, Sharma's protocol[24] of transforming an allylic alcohol directly to the corresponding hydrocarbon was applied. Thus, treatment of **7** with nickel boride, generated

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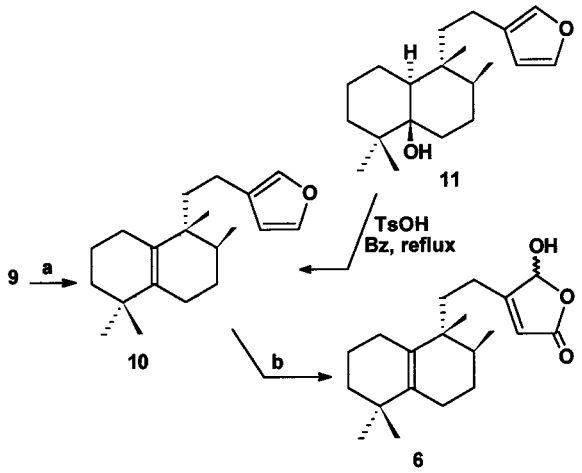
Scheme 2[a]



[a] Key: (a) HCl−HOAc (1:4), 60 °C (85%); (b) O_2, Rose Bengal, DIPEA, CH_2Cl_2, −78 °C, (90%).

in situ, gave **9** as a single product in 73% yield. Treatment of the acetate **8** with nickel boride also led to the desired compound **9** in 75% yield. Following the same procedure described above for **7**, photosensitized oxygenation of **9** gave **5** in 72% yield. Physical and spectroscopic data of the synthetic product were in good agreement with those reported for the natural product,[2−13] except for the expected difference in the optical rotation, which was $[\alpha]_D$ +30.0 (*c* 1.7, $CHCl_3$) {lit.[7] $[\alpha]_D$ − 48.7° (*c* 3.02, $CHCl_3$)}.

Compound **10**, required for the synthesis of **6**, was obtained in 85% yield through acid-catalyzed rearrangement of **9** using acetic acid and hydrochloric acid at 60 °C (Scheme 2). Spectroscopic data of **10** were in good agreement with those reported in the literature for dehydroambliol-B, a dehydration product obtained from the marine diterpene ambliol-B (**11**) by treatment with p-TsOH in benzene.[25,26]

Finally, photosensitized oxygenation of **10** furnished the desired compound **6** in 90% yield. Spectroscopic data of **6** were also in good agreement with those reported in the literature for the enantiomer, except for the expected difference in the optical rotation, which was $[\alpha]_D$ −35.4° (*c* 0,24, $CHCl_3$) {lit.[5] $[\alpha]_D$ + 21.0° (*c* 0.54, $CHCl_3$)}.

Compounds **3**, **5**, and **6** were evaluated for antitubercular activity. Only **5** showed significant activity according to the TAACF protocol (12.5 μg mL^{-1}), with 85% inhibition of *Mycobacterium tuberculosis*.[27]

Experimental Section

General Experimental Procedures. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 and 75 MHz, respectively, with a Bruker AC 300/P spectrometer (internal standard TMS). IR spectra were recorded on a Perkin-Elmer 1600 series FT IR. MS spectra were obtained at 70 eV on an HP-5990/5970 system equipped with a J&W Scientific DB-5 fused silica capillary column (30 m × 0.25 mm × 0.25 μm). Elemental analyses were performed with a Perkin-Elmer CHN analyzer. Optical rotations were measured with a Carl Zeiss photoelectric polarimeter.

{**(4aα,6*β*,8a*β*)-1-Hydroxymethyl-5(*R*)-[2-(3-furanyl)ethyl]-5,6,8a-trimethyl-3,4, 4a,5,6,7,8,8a-octahydronaphthalene**} (**7**). A 1.0 M solution of DIBAL (3.7 mL, 3.7 mmol) was added to a stirred solution of **2b** (558 mg, 1.7 mmol) in dry toluene (20 mL), at −78 °C, and the reaction mixture was warmed to 0 °C and stirred for 2 h. Saturated aqueous ammonium chloride (8 mL) was added, and the reaction mixture was extracted with ethyl ether (3 × 30 mL), washed with brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (petroleum ether−ethyl acetate; 9:1) to give **7** (500 mg; 98%) as a colorless oil: $[\alpha]^{23}_D$ +18.3 ($CHCl_3$, *c* 1.49); IR (neat) ν_{max} 3422, 2926, 2867, 1654, 1639, 1458, 1383, 1264, 1024, 873, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (3H, s, H-20), 0.83 (3H, d, *J* = 6.4 Hz, H-17), 1.08 (3H, s, H-19), 1.20−1.80 (11H, m), 2.00−2.40 (4H, m), 4.10 (2H, d, *J* = 1.5 Hz, H-18), 5.57 (1H, t, *J* = 1.7 Hz, H-3), 6.26 (1H, t, *J* = 1.0 Hz, H-14), 7.20 (1H, bs, H-16), 7.35 (1H, t, *J* = 1.7 Hz, H-15); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.2 (s, C-4), 142.9 (d, C-15), 138.6 (d, C-16), 125.9 (s, C-13), 122.3 (d, C-3), 111.2 (d, C-14), 63.1 (t, C-18), 46.4 (d, C-10), 38.8 (s, C-9), 38.6 (t, C-11), 37.5 (s, C-5), 36.4 (t, C-6), 36.3 (d, C-8), 27.3 (t, C-7), 26.6 (t, C-2), 21.4 (q, C-19), 18.3 (q, C-20), 18.2 (t, C-1), 18.2 (t, C-12), 16.0 (q, C-17); MS (*m*/*z*, %) (M+) 302(16), 271(16), 189(50), 94(58), 81(100), 41(70); *anal*. C 79.29%, H 9.74%, calcd for $C_{20}H_{30}O_2$, C 79.42%, H 9.99%.

{**(4aα,6*β*,8a*β*)-1-Acetoxymethyl-5(*R*)-[2-(3-furanyl)ethyl]-5,6,8a-trimethyl-3,4, 4a,5,6,7,8,8a-octahydronaphthalene**} (**8**). Acetic anhydride (0.1 mL, 0.6 mmol) was added to a solution of **7** (75 mg, 0.2 mmol) in dry pyridine (1 mL), and the mixture was stirred overnight at room temperature. Cold water (10 mL) was added, and the reaction mixture was extracted with ethyl ether (3 × 30 mL). The organic phase was washed with 5% HCl (2 × 10 mL) and then with brine until pH 7.0 and dried over anhydrous sodium sulfate. After removal of solvent under reduced pressure and purification of the residue by column chromatography (silica gel, *n*-hexane), compound **8** (72 mg, 85%) was obtained as a colorless oil. $[\alpha]^{23}_D$ +26.3 ($CHCl_3$, *c* 1.94); IR (neat) ν_{max} 2925, 2856, 1740, 1450, 1384, 1239, 1026, 873, 780; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (3H, s, H-20), 0.83 (3H, d, *J* = 6.5 Hz, H-17), 1.08 (3H, s, H-19), 1.30−1.80 (10H, m), 1.98−2.40 (4H, m), 2.07 (3H, s, OAc), 4.53 (2H, t, *J* = 2.7 Hz, H-18), 5.60 (1H, t, *J* = 3.5 Hz, H-3), 6.26 (1H, d, *J* = 1.8 Hz, H-16), 7.20 (1H, bs, H-14), 7.34 (1H, t, *J* = 1.6 Hz, H-15); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3 (s, C=O), 142.9 (s, C-4), 142.9 (d, C-15), 138.6 (d, C-16), 126.2 (d, C-3), 125.9 (s, C-13), 111.2 (d, C-14), 65.1 (t, C-18), 46.3 (d, C-10), 38.8 (s, C-9), 38.6 (t, C-11), 37.9 (s, C-5), 36.3 (d, C-8), 36.2 (t, C-6), 27.2 (t, C-7), 26.7 (t, C-2), 21.3 (q, C-19), 21.2 (q, H_3C−CO), 18.2 (t, C-1), 18.2 (t, C-12), 18.1 (q, C-20), 16.0 (q, C-17); *anal*. C 76.56%, H 9.14%, calcd for $C_{22}H_{32}O_3$, C 76.70%, H 9.36%.

{**(4aα,6*β*,8a*β*)-5(*R*)-[2-(3-Furanyl)ethyl]-1,5,6,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene**} (**9**). Anhydrous nickel chloride (622 mg, 4.8 mmol) and sodium borohydride (363 mg, 9.6 mmol) were added to a solution of **7** (104 mg, 0.3 mmol) in diglyme (15 mL) at 0 °C, whereupon a black precipitate formed. The mixture was stirred for 6 h, then diluted with dichloromethane (20 mL), and filtered through a pad of Celite, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (*n*-hexane−ethyl ether; 95:5) to give **9** (72 mg, 73%) as a colorless oil. $[\alpha]^{23}_D$ +21.3 ($CHCl_3$, *c* 2.64); IR (neat) ν_{max} 2925, 2866, 1458, 1382, 1160, 1025, 872, 778 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.73 (3H, s, H-20), 0.83 (3H, d, *J* = 6.3 Hz, H-17), 0.99 (3H, s, H-19), 1.10−1.90 (10H, m), 1.56 (3H, d, *J* = 1.6 Hz, H-18), 2.00−2.40 (4H, m), 5.11 (1H, bs, H-3), 6.14 (1H, s, H-16), 7.10 (1H, bs, H-14), 7.24 (1H, t, *J* = 1.5 Hz, H-15); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 143.7 (s, C-4), 142.3 (d, C-15), 138.0 (d, C-16), 125.2 (s, C-13), 120.6 (d, C-3), 110.7 (d, C-14), 46.1 (d, C-10), 38.5 (t, C-11), 38.4 (s, C-9), 37.9 (s, C-5), 36.6 (t, C-6), 36.2 (d, C-8), 27.4 (t, C-7), 26.7 (t, C-2), 19.8 (q, C-19), 18.2 (t, C-1), 18.2 (t, C-12), 18.2 (q, C-20), 17.9 (q, C-18), 16.1 (q, C-17); MS (*m*/*z*, %) (M+) 286(30), 271(35), 191(60), 107(62), 95(100), 81(80), 41(70); *anal*. C 83.57%, H 10.73%, calcd for $C_{20}H_{30}O$, C 83.86%, H 10.56%.

{**(4aα,6*β*,8a*β*)-1-Hydroxymethyl-5(*R*)-[2-(2,5-dihydro-5-hydroxy-2-oxo-4-furanyl)ethyl]-5,6,8a-trimethyl-3,4,-4a,5,6,7,8,8a-octahydronaphthalene**} (**4**). Oxygen was bubbled through a solution of **7** (80 mg, 0.3 mmol) in CH_2Cl_2 (20 mL), diisopropylamine (0.4 mL), and Rose Bengal on polystyrene (3 mg) and irradiated with a tungsten lamp (250 W) at −78 °C for 6 h. The reaction mixture was filtered through a pad of Celite, and the residue was purified by silica

gel column chromatography ($CHCl_3$−MeOH; 99:1) to give **4** (66 mg, 75%) as an oil: IR (neat) ν_{max} 3372, 2926, 1756, 1648, 1458, 1129, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (3H, s, H-20), 0.81 (3H, d, J = 6.0 Hz, H-17), 1.08 (3H, s, H-19), 1.20−2.50 (15H, m), 4.10 (2H, s, H-18), 4.55 (1H, br, OH), 5.57 (1H, s, H-3), 5.84 (1H, s, H-14), 6.00 (1H, s, H-16); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.5 (s, C-15), 170.4 (s, C-13), 142.3 (s, C-4), 136.8 (d, C-3), 117.0 (d, C-14), 99.1 (d, C-16), 63.1 (t, C-18), 46.5 (d, C-10), 38.7 (s, C-9), 37.5 (s, C-5), 36.3 (d, C-8), 35.7 (t, C-6), 34.8 (t, C-11), 27.1 (t, C-7), 27.0 (t, C-2), 21.2 (t, C-12), 20.6 (q, C-19), 18.1 (q, C-20), 17.4 (q, C-1), 15.9 (C-17); *anal*. C 71.59%, H 9.14%, calcd for $C_{20}H_{30}O_4$, C 71.82%, H, 9.04%.

{**(4aα,6*β*,8a*β*)-5(*R*)-[2-(2,5-Dihydro-5-hydroxy-2-oxo-4-furanyl)ethyl]-1,5,6,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene**} (**5**). Using the same procedure as described above for **7**, reaction of **9** (30 mg, 0.1 mmol) furnished hydroxybutenolide **5** (24 mg, 72%) as an oil: $[\alpha]^{23}_D$ +30.0 (*c* 1.7, $CHCl_3$); IR (neat) ν_{max} 3336, 2956, 1759, 1737, 1647, 1448, 1130, 953, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.72−0.98 (2H, m), 0.77 (3H, s, H-20), 0.81 (3H, d, J = 6.0 Hz, H-17), 1.01 (3H, s, H-19), 1.10−1.84 (9H, m), 1.58 (3H, d, J = 1.5 Hz, H-18), 1.90−2.40 (3H, m), 4.58 (1H, br, OH), 5.19 (1H, s, H-3), 5.84 (1H, s, H-14), 6.01 (1H, s, H-16); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.6 (s, C-15), 170.4 (s, C-13), 144.4 (s, C-4), 122.4 (d, C-3), 117.0 (d, C14), 99.1 (d, C-16), 46.5 (d, C-10), 38.7 (s, C-9), 38.7 (s, C-5), 38.2 (t, C-6), 36.7 (d, C-8), 34.8 (t, C-11), 27.4 (t, C-7), 26.5 (t, C-2), 21.4 (t, C-12), 19.9 (q, C-19), 18.3 (t, C-1), 18.2 (q, C-17), 18.0 (q, C-18), 16.0 (q, C-20); MS (*m*/*z*, %) (M+) 318(25), 275(70), 191(80), 149(70), 123(100), 107(98), 41-(96); *anal*. C 75.29%, H 9.44%, calcd for $C_{20}H_{30}O_3$, C 75.43%, H, 9.50%.

(6*β*)-5(*R*)-[2-(3-Furanyl)ethyl]-1,1,5,6-tetramethyl-1,2,3,4,5,6,7,8-octahydronaphthalene} (**10**). A solution of **9** (35 mg, 0.1 mmol) in acetic acid (0.4 mL) and concentrated hydrochloric acid (0.1 mL) was heated at 60 °C. After stirring for 12 h, water (5 mL) was added and the mixture was extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with brine and dried over anhydrous sodium sulfate. After removal of solvent under reduced pressure and purification of the residue by column chromatography (silica gel, *n*-hexane), compound **10** (30 mg, 85%) was obtained as a colorless oil: $[\alpha]^{23}_D$ −26.0 ($CHCl_3$, *c* 1.47); IR (film) 2956, 1495, 1452, 1363, 1028, 730 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (3H, s, H-20), 0.87 (3H, d, J = 6.9 Hz, H-17), 0.98 (3H, s, H-18), 0.99 (3H, s, H-19), 1.10−1.90 (11H, m), 2.00−2.40 (4H, m), 6.13 (1H, bs, H-14), 7.09 (1H, bs, H-16), 7.23 (1H, bs, H-15); ^{13}C NMR ($CDCl_3$, 75 MHz,) δ 142.9 (d, C-15), 138.8 (s, C-5), 137.5 (d, C-16), 132.8 (s, C-10), 126.1 (s, C-13), 111.3 (d, C-14), 40.9 (s, C-9), 40.3 (t, C-3), 36.8 (t, C-11), 34.7 (s, C-4), 33.8 (d, C-8), 29.4 (q, C-18), 27.8 (q, C-19), 27.5 (t, C-7), 26.2 (t, C-6), 25.6 (t, C-1), 21.2 (q, C-20), 20.3 (t, C-12), 19.9 (t, C-2), 16.3 (q, C-17); *anal*. C 83.69%, H 10.34%, calcd for $C_{20}H_{30}O$, C 83.86%, H 10.56%.

{**(6*β*)-5(*R*)-[2-(2,5-Dihydro-5-hydroxy-2-oxo-4-furanyl)-ethyl]-1,1,5,6-tetramethyl-1,2,3,4,5,6,7,8-octahydronaphthalene**} (**6**). Using the same procedure as described for **7**, reaction of **10** (30 mg, 0.1 mmol) furnished hydroxybutenolide **6** (30 mg, 90%) as an oil: $[\alpha]^{23}_D$ −35.4 ($CHCl_3$, *c* 0.24); IR (film) 3386, 2944, 1753, 1648, 1256, 1128, 738 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.86 (3H, d, J = 6.6 Hz, H-17), 0.87 (3H, s, H-20), 0.97 (3H, s, H-18), 0.99 (3H, s, H-19), 1.10−2.50 (15H, m), 4.25 (1H, bs, OH), 5.84 (1H, s, H-14), 6.00 (1H, bs, H-16); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.3 (s, C-15), 170.6 (s, C-13), 138.5 (s, C-5), 131.3 (s, C-10), 117.0 (d, C-14), 98.9 (d, C-16), 40.7 (s, C-9), 39.8 (t, C-3), 34.6 (s, C-4), 33.7 (d, C-8), 32.8 (t, C-11), 29.2 (q, C-18), 27.6 (q, C-19), 27.1 (t, C-7), 25.7 (t, C-6), 25.3 (t, C-1), 22.7 (t, C-12), 20.9 (q, C-20), 19.9 (t, C-2), 16.2 (q, C-17); *anal*. C 75.22%, H 9.24%, calcd for $C_{20}H_{30}O_3$, C 75.43%, H 9.50%.

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