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Short Report

Synthesis of *Ent*-16-hydroxycleroda-4(18),13-dien-15,16-olide and *Ent*-cleroda-4(18),13-dien-15,16-olide from (+)-Hardwickiic Acid

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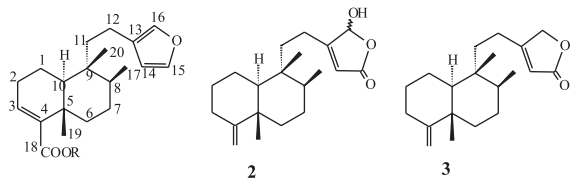
As configurações absolutas de dois diterpenos butenolidos naturais foram confirmadas através da síntese do *ent*-16-hidroxicleroda-4(18),13-dien-15,16-olida (**2**) e ent-cleroda-4(18),13-dien-15,16-olida (**3**), enantiômeros de produtos naturais, a partir do ácido (+)-hardwickiico (**1**).

The absolute configurations of two natural diterpene butenolides were confirmed through the synthesis of *ent*-16-hydroxycleroda-4(18),13-dien-15,16-olide (**2**) and ent-cleroda-4(18),13-dien-15,16-olide (**3**), enantiomers of the natural products, starting from (+)-hardwickiic acid (**1**).

Keywords: (+)-hardwickiic acid, clerodane, butenolide, absolute configuration

Introduction

The occurrence of natural clerodane diterpene butenolides and hydroxybutenolides has been reported in plants of the genera *Polyalthia*,[1-10] *Acritopappus*,[11] *Premna*,[12] and *Cyathocalyx*,[13] as well as their biological properties as antifeedants,[1] cytotoxicity to tumor cell cultures,[2,9] toxicity against *Artemia salina*[2,13] and *Aedes aegypti*,[13] febrifuges,[3] antimicrobials,[5,12] chewing sticks for sterilizing milk container,[12] and diuretics.[14] Syntheses of some biologically active clerodanolides and *ent*-halimanolides were recently published[15,16] showing the importance of this new class of terpenoids. In connection with a previous study on the synthesis of some biological active hydroxybutenolide derivatives and regarding the use of the readily available methyl (+)-hardwickiate (**1b**) for the synthesis of natural products,[14,17,18] the clerodanes **2** and **3**, enantiomers of two natural products,[4,10] have been synthesized (Figure 1). Since only the relative stereochemistry was reported in the literature, the syntheses of **2** and **3** allowed to elucidate the absolute stereochemistry of the compounds isolated from *Polyalthia longifolia* Thw.[4]



1a R = H
1b R = CH_3

Figure 1. Structures of (+)-hardwickiic acid (**1**) and butenolides **2** and **3**.

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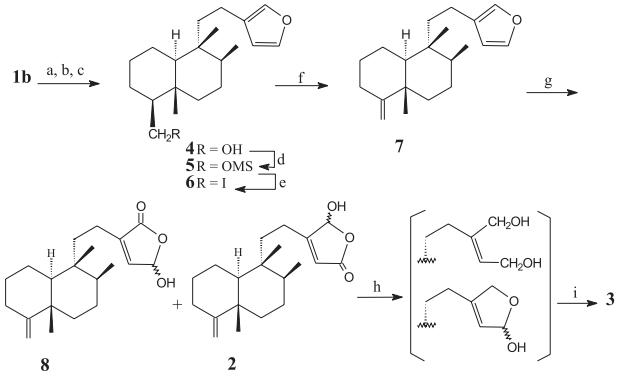
Results and Discussion

The reduction of carbomethoxy group of **1b** to the corresponding methyl group and isomerization of endocyclic double bond to exocyclic double bond in order to obtain a desired A ring functionality of the structures **2** and **3**, a dehydration reaction of the known alcohol **4**[18] was considered. Although the alcohol **4** was prepared previously in a reasonable yield through the reduction of (+)-methyl hardwickiate (**1b**) using an excess of sodium in propan-1-ol, a mixture with corresponding carboxylic acid was always obtained.[18] Thus, the crude product was first treated with diazomethane and then submitted to the reduction with lithium aluminum hydride to furnish the desired alcohol **4** in 59% overall yield. (Scheme 1)

In a previous study[19] it was observed that the elimination reaction of the corresponding sulfonic ester (-OTs or -OMs) using basic conditions (DBU, $^tBuO^-$ K^+) led to the desired olefin in a low yield and recovering the starting material. To detour this problem the dehydroiodination reaction was considered. Mesylation of alcohol **4** with methanesulfonyl chloride followed by treatment with sodium iodide gave the corresponding iodide **6** in 50% yield. Next, the dehydroiodination reaction of **6** was performed using silver fluoride[20] to furnish olefin **7** in 69% yield.



Scheme 1. Reagents and conditions: a) Na°/propan-1-ol, reflux for 17 h; b) CH_2N_2, Et_2O; c) $LiAlH_4$, Et_2O, rt, 1 h, 59% (3 steps); d) MsCl, Py, rt, 19 h, 71%; e) NaI, acetone, reflux for 26 h, 71%; f) AgF, Py, rt, 69%; g) O_2, DIPEA, hv, Rose bengal, CH_2Cl_2, -78 °C, 3 h, 2 and 8 (2:1), 71%; h) treatment of 2 with $NaBH_4$, MeOH, rt, 4 h; i) PCC, CH_2Cl_2, rt, 1 h, 71% (2 steps).

Following this sequence, the synthesis of the hydroxybutenolide moiety from the furan ring was carried out using previously described procedures.[17,21] The photooxygenation reaction of **7** in CH_2Cl_2 at –78 °C in the presence of Rose Bengal and diisopropylethylamine (DIPEA), furnished the expected hydroxybutenolide **2** and the regioisomer **8** (2:1) in a combined 71% yield. After chromatographic separation, fractions containing pure **2** and a mixture of **2** and **8** were obtained. The ^{1}H NMR spectra of **2** showed signals at δ 5.98 (H-16) and at δ 5.81 (H-14) which were in good agreement with those observed in the literature (δ 6.00 and 5.80, respectively) for the enantiomer.[4] Other spectroscopic and physical data of **2** were also in agreement with those reported for the enantiomer, except the sign of optical rotation, which was $[\alpha]_D^{25}$ -15.9° ($CHCl_3$, c 1.9) {lit.[4] $[\alpha]_D^{25}$ +10.0° ($CHCl_3$, c 1.2); lit.[10] $[\alpha]_D^{25}$ +19.5° ($CHCl_3$, c 0.64)}. The purification of compound **8** showed to be very difficult by column chromatography and thus, a fraction enriched with **8** was analyzed by ^{1}H NMR. Two signals observed at δ 6.73 (H-14) and at δ 6.00 (H-15) confirmed the α-substituted hydroxybutenolide moiety and are in agreement with those observed in the literature for the model compound.[21] For the synthesis of lactone **3**, hydroxybutenolide **2** (or a mixture containing **2** and **8**) was treated with sodium borohydride in methanol according to a described procedure.[10] After work-up and purification of the crude product by silica gel column chromatography, lactone **3** was obtained in only 21% yield, along with an inseparable mixture of the over-reduction products, the diol and lactol. In order to improve the yield, the crude product, after reduction of **2** with sodium borohydride, was treated with PCC. In this manner the desired lactone **3** was obtained in 71% yield from **2**. Lactone **3** was characterized through physical and spectroscopic analyses and showed good agreement with data reported for the enantiomer,[4] except for the sign of optical rotation, which was $[\alpha]_D^{25}$ -2.7° ($CHCl_3$, c 0.9) {lit.[4] $[\alpha]_D^{25}$ +15.2° (MeOH, c 1.9)}.

Conclusions

Two enantiomers of natural clerodane, butenolide **2** and lactone **3,** were synthesized from known (+)-hardwickiic acid (**1**). Although the absolute value of the optical rotation obtained for lactone **3**, in different solvent, was smaller than reported in the literature, the observed sign is an indicative that natural product isolated from *Polyalthia* species has a normal clerodane skeleton, as well as butenolide **2**.

Experimental

General experimental procedures

The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 and 75.5 MHz, respectively, with a Varian Gemini 300 instrument, and at 500 and 125.7 MHz, respectively, with a Varian Inova 500 MHz spectrometer (internal standard TMS). The assignments of carbon signals were made by means of 2D NMR ^{1}H and ^{13}C single bond and multiple bond correlation studies. IR spectra were recorded on a Perkin-Elmer 1600 series FT IR. MS spectra were obtained at 70 eV on an HP-5890/5970 equipped with a J & W Scientific DB-5 fused silica column (30 m x 0.25 mm x 0.25 μm) or HP-5 column (30 m x 0.25 mm x 0.25 μm). High-resolution mass spectra (HRMS) were recorded with a VG 7070E spectrometer. Optical rotations were measured with a POLAMAT photoelectric polarimeter.

*Ent-(4S)-cleroda-15(16)-oxo-13(16),14-dien-18-ol (**4**)*

Small pieces of sodium (641 mg, 27.9 mmol) were added to a stirred solution of **1b** {$[\alpha]_D^{25}$ +121.5° ($CHCl_3$, *c* 1.4)} (107 mg, 0.3 mmol) in dry propan-1-ol (10 mL), and the reaction mixture was stirred at reflux temperature for 17 h under nitrogen. Excess sodium was destroyed by the careful addition of ethanol at 0 °C. Water (20 mL) was added, the solution was acidified by adding 1 mol L^{-1} HCl (to pH ~ 2-3) and the mixture extracted with ethyl ether (3 x 30 mL). The organic phase was washed with brine and dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was esterified with an excess of diazomethane in ethyl ether at 0 °C. The crude esterified product was dissolved

in dry ethyl ether (12 mL) and was added to a suspension of $LiAlH_4$ (3.3 mg, 0.9 mmol) in dry ethyl ether (5 mL). The reaction mixture was stirred for 1 h at room temperature under nitrogen. Excess $LiAlH_4$ was then destroyed by the careful addition of 10% aqueous NaOH. The ethereal solution was dried over anhydrous $MgSO_4$, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (hexane-EtOAc, 9:1) to give **4** (58.3 mg, 59%) as a colorless oil: $[\alpha]_D^{25}$ + 50.8° (*c* 2.46, $CHCl_3$). The spectroscopic data were in good agreement with those reported previously.[18]

*Mesylate **5***

Methanesulfonyl chloride (1 mL, 13 mmol) was added dropwise to a solution of **4** (166.7 mg, 0.6 mmol) in dry pyridine (4 mL) at 0 °C and the mixture was stirred for 19 h at room temperature under nitrogen. Ethyl acetate (25 mL) was added and the reaction mixture was washed with 5% aqueous HCl (3 x 30 mL) and saturated $NaHCO_3$ solutions (3 x 30 mL). The organic phase was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuum*. The residue was chromatographed on silica gel (hexane-EtOAc, 9:1) to give **5** (148.0 mg, 71%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.71 (3H, s, H-20), 0.82 (3H, d, *J* 6.7 Hz, H-17), 0.87 (3H, s, H-19), 1.00 - 2.02 (15H, m), 2.10 - 2.38 (2H, m), 2.99 (3H, s, -SC$\underline{H}_3$), 3.89 (1H, dd, *J* 9.3; 9.5 Hz, H-18a), 4.40 (1H, dd, *J* 3.7; 9.5 Hz, H-18b), 6.25 (1H, brs, H-14), 7.20 (1H, brs, H-16), 7.34 (1H, brs, H-15).

*Iodide **6***

NaI (560.0 mg, 3.7 mmol) was added to a solution of compound **5** (134.2 mg, 0.4 mmol) in dry acetone (6 mL), and the reaction mixture was stirred at reflux temperature for 26 h under nitrogen. The solvent was evaporated, H_2O (20 mL) was added and the mixture was extracted with ethyl ether (4 x 30 mL). The ethereal solution was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuum*. The residue was chromatographed on silica gel (hexane–EtOAc, 96:4) to obtain compound **6** (145.1 mg, 71%) as colorless oil. IR (neat) ν_{max}/ cm^{-1}: 2926, 2872, 1447, 1384, 1025, 873, 778, 599; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.71 (3H, s, H-20), 0.81 (3H, d, *J* 6.6 Hz, H-17), 0.81 (3H, s, H-19), 1.00 - 1.85 (15H, m), 2.00 - 2.36 (2H, m), 2.79 (1H, dd, *J* 9.5; 11.0 Hz, H-18), 3.58 (1H, dd, *J* 2.4; 9.5 Hz, H-18), 6.24 (1H, brs, H-14), 7.19 (1H, brs, H-16), 7.34 (1H, brs, H-15); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 11.2 (CH_2, C-12), 13.9 (CH_3, C-19), 16,8 (CH_3, C-17), 18.2 (CH_2, C-1), 18.3 (CH_3, C-20), 21.7 (CH_2, C-2), 26.8 (CH_2, C-3), 27.3 (CH_2, C-7), 28.3 (CH_2, C-11), 36.6 (CH, C-8), 38.7 (CH_2, C-6), 39.0 (CH_2, C-18), 39.4 (C, C-5), 39.5 (C, C-9), 49.8 (CH, C-10), 55.4 (CH, C-4), 111.0 (CH, C-14), 125.6 (C, C-13), 138.3 (CH, C-16), 142.6 (CH, C-15); EIMS *m/z* 414 [M]$^{+\cdot}$ (26), 319 (100), 191 (66), 149 (45), 123 (38), 96 (86), 81 (81), 67 (51), 55 (54).

*Ent-cleroda-15(16)-oxo-4(18),13(16),14-triene (**7**)*

AgF (101.2 mg, 0.8 mmol) was added to a solution of compound **6** (18.4 mg, 0.04 mmol) in dry pyridine (6.0 mL), and the reaction mixture was stirred for 23 h at room temperature under nitrogen. The crude product was filtered through a pad of Celite (5 cm) on silica gel using ethyl ether as eluent. The solvent was evaporated *in vacuum* and the resulting product was purified by column chromatography on silica gel (hexane-EtOAc, gradient of polarity), to give compound **7** (8.8 mg, 69%) as colorless oil. $[\alpha]_D^{25}$ -20.0° (*c* 1.0, $CHCl_3$); IR (neat) ν_{max}/ cm^{-1}: 3088, 2927, 2863, 1779, 1635, 1445, 1383, 1064, 1025, 891, 873; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (3H, s, H-20), 0.82 (3H, d, *J* 4.0 Hz, H-17), 0.84 (3H, s, H-19), 1.14 - 1.94 (14H, m), 2.06 - 2.36 (2H, m), 4.51 (2H, s, H-18), 6.25 (1H, brs, H-14), 7.25 (1H, brs, H-16), 7.33 (1H, brs, H-15); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.1 (CH_3, C-17); 18.1 (CH_3, C-20), 18.1 (CH_2, C-12), 20.9 (CH_3, C-19), 21.7 (CH_2, C-1), 27.5 (CH_2, C-7), 28.7 (CH_2, C-2), 33.1 (CH_2, C-3), 36.7 (CH, C-8), 37.4 (CH_2, C-6), 38.4 (CH_2, C-11), 39.3 (C, C-9), 40.1 (C, C-5), 48.7 (CH, C-10), 102.5 (CH_2, C-18), 111.0 (CH, C-14), 125.7 (C, C-13), 138.4 (CH, C-16), 142.6 (CH, C-15), 160.7 (C, C-4); EIMS *m/z* 286 [M]$^{+\cdot}$ (10), 191 (82), 149 (45), 135 (29), 95 (100), 55 (24); HREIMS *m/z* 286.2285 (calc. for $C_{20}H_{30}O$, 286.2297).

*Ent-16-hydroxycleroda-4(18),13-dien-15,16-olide (**2**) and ent-15-hydroxycleroda-4(18),13-dien-16,15-olide (**8**)*

Oxygen was bubbled through a solution of **7** (11 mg, 0.04 mmol) in CH_2Cl_2 (25 mL), diisopropylamine (60 μL, 0.3 mmol), and Rose Bengal on polystyrene in a catalytic amount was added and the mixture was irradiated with a halogen lamp (300W) at -78 °C for 3 h. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane–EtOAc, 85:15) to give a mixture of regioisomers **2** and **8** (2:1) (8.7 mg, 71%). After repeated chromatography, a fraction containing 4 mg of pure **2** could be obtained and was characterized. Compound **2** was obtained as colorless oil. $[a]_D^{25}$ -15.9° (*c* 1.9, $CHCl_3$); IR (neat) ν_{max}/ cm^{-1}: 3407, 3291, 2923, 2856, 1725, 1640, 1153, 940, 894, 853; ^{1}H

NMR ($CDCl_3$, 300 MHz) δ 0.79 (3H, s, H-20), 0.81 (3H, d, *J* 5.9 Hz, H-17), 1.06 (3H, s, H-19), 1.10 - 2.40 (16H, m), 4.51 (2H, brs, H-18), 5.81 (1H, s, H-14), 5.98 (1H, s, H-16); ^{13}C NMR ($CDCl_3$, 75.5 MHz) d 16.0 (CH_3, C-17), 18.0 (CH_3, C-20), 20.8 (CH_3, C-19), 21.3 (CH_2, C-1), 21.7 (CH_2, C-12), 27.3 (CH_2, C-7), 28.6 (CH_2, C-2), 32.9 (CH_2, C-3), 34.7 (CH_2, C-11), 36.7 (CH, C-8), 37.2 (CH_2, C-6), 39.2 (C, C-9), 40.0 (C, C-5), 48.7 (CH, C-10), 99.0 (CH, C-16), 102.8 (CH_2, C-18), 117.0 (CH, C-14), 160.2 (C, C-4), 170.4 (C, C-13), 171.5 (C, C-15); EIMS *m/z* 318 $[M]^{+\cdot}$ (5), 191 (71), 163 (21), 135 (60), 95 (100), 55 (29); HREIMS *m/z* 318.2181 (calc. for $C_{20}H_{30}O_3$, 318.2195); Compound **8** (main signals): ^1H NMR ($CDCl_3$, 300 MHz) δ 6.00 (1H, H-15), 6.73 (1H, H-14), 4.44 (2H, br, H-18).

*Ent-cleroda-4(18),13-dien-15,16-olide (**3**)*

To a stirred solution of $NaBH_4$ (29 mg, 0.8 mmol) in MeOH (0.5 mL) was added a solution of **2** (18 mg, 0.06 mmol) in MeOH (2.5 mL). The resulting solution was stirred at room temperature under nitrogen for 4 h after which the solvent was removed under vacuum. The crude product was dissolved in dry CH_2Cl_2 (2 mL) and was added to a solution of PCC (22 mg, 0.1 mmol) in dry CH_2Cl_2. The reaction mixture was stirred for 1 h at room temperature under nitrogen. The resulting product was filtered through silica gel with a layer of alumina on the top of the column, using ethyl ether as eluent. After removal of solvent under reduced pressure and purification of the residue by column chromatography (silica gel, hexane–EtOAc, 92:8), compound **3** was obtained (12 mg, 71%) as colorless oil. $[\alpha]^2_{D}{}^5$ -2.7 ^{o} (*c* 0.9, $CHCl_3$); IR (neat) ν_{max}/ cm $^{-1}$: 2927, 2866, 1779, 1635, 1449, 1382, 1167, 1023, 890; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.80 (3H, s, H-20), 0.83 (3H, d, *J* 6.2 Hz, H-17), 1.07 (3H, s, H-19), 1.10 - 1.98 (14H, m), 2.00 - 2.40 (2H, m), 4.53 (2H, d, *J* 1.5 Hz, H-18), 4.73 (2H, d, *J* 1.5 Hz, H-16), 5.82 (1H, t, *J* 1.6 Hz, H-14); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.1 (CH_3, C-17), 18.1 (CH_3, C-20), 20.9 (CH_3, C-19), 21.9 (CH_2, C-1), 22.3 (CH_2, C-2), 22.3 (CH_2, C-12), 27.4 (CH_2, C-7), 28.7 (CH_2, C-3), 36.8 (CH, C-8), 37.3 (CH_2, C-6), 37.3 (CH_2, C-11), 39.3 (C, C-5), 40.1 (C, C-9), 48.8 (CH, C-10), 73.1 (CH_2, C-16), 102.8 (CH_2, C-18), 114.9 (CH, C-14), 160.0 (C, C-4), 170.9 (C, C-13), 173.9 (C, C-15); EIMS *m/z* 302 $[M]^{+\cdot}$ (9), 191 (78), 135 (73), 95 (100), 55 (49); HREIMS *m/z* 302.2245 (Calc. for $C_{20}H_{30}O_2$, 302.2246).

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