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SYNTHESIS OF (−)-UGANDENSIDIAL

MANUEL CORTES,* IVAN RAZMILIC, and JOSE LOPEZ

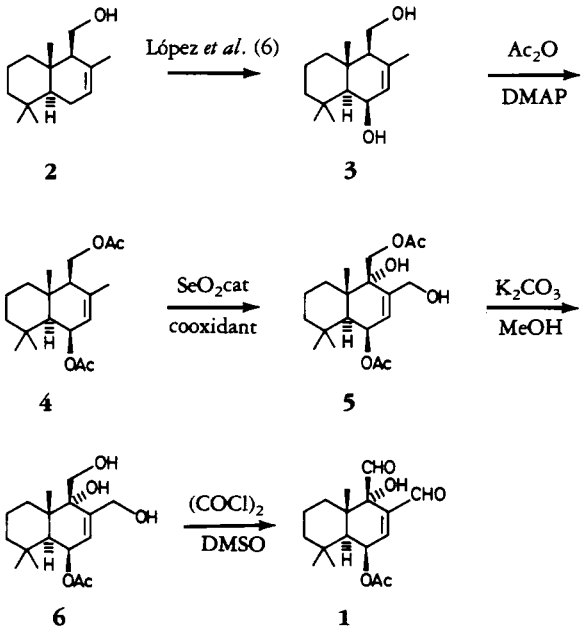
Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 6177, Santiago, Chile

ABSTRACT.—The first synthesis of optically active ugandensidial [**1**] from the sesquiterpene diol **3** is described.

Ugandensidial (1,2) is a sesquiterpene which has been isolated from the bark of the East African medicinal plants *Warburgia ugandensis* and *Warburgia stuhlmanii* (Canellaceae). This product as well as some related dialdehydes exhibits a strong antifeedant activity against the African army worm *Spodoptera exempta* and *Spodoptera littoralis* (3). Racemic ugandensidial has been synthesized by Naito *et al.* (4) and by White and Burton (5).

These syntheses suffer some shortcomings. One of them (4) starts with a readily available precursor but involves a lengthy procedure. The other (5) is more efficient but furnished the racemic product. Because there is a need for the production of nonracemic drimane antifeedants, we now report the first synthesis of (−)-ugandensidial [**1**]. The starting material was the diol **3**, which was prepared via a known route from (−)-drimenol [**2**] (6).

The synthesis of (−)-ugandensidial [**1**] is outlined in Scheme 1. Acetylation of **3** with Ac_2O in pyridine and a catalytic amount of 4-(dimethylaminopyridine) gave the diacetate **4** in 75% yield. Allylic oxidation of **4** was achieved in dioxane with a catalytic amount of selenium dioxide and bis(4-methoxyphenyl) selenoxide as co-oxidant, according to Ogura's method (7). The dialcohol **5** (46%) was obtained. The ir spectrum of **5** shows hydroxyl and ester absorptions at 3500 and 1470 cm^{-1}. The geminal protons of the primary al-



SCHEME 1

cohol appear as a complex signal at δ 4.25 partially superimposed with the CH_2-OAc protons. Partial saponification of **5** with K_2CO_3/MeOH gave the triol **6** in almost quantitative yield. The geminal protons of the allylic alcohol appear as a broad singlet at δ 3.78, and the geminal protons of the other primary alcohol appear as an AB system, δ_A 4.16 (J = 12 Hz), δ_B 4.28 (J = 12 Hz). Oxidation of **6** with oxalyl chloride/DMSO (8) afforded (−)-ugandensidial [**1**] in 77% yield. The physical properties (including optical rotation) and spectroscopic data were almost identical with those of natural ugandensidial (1).

The synthesis of (−)-**1** was performed in twelve steps with an overall yield of 10% starting from known (−)-drimenol. This semisynthetic approach is highly competitive with respect to the syntheses of White and Burton (5) and Naito *et al.* (4), which had overall yields of 7.9% and 0.04%, respectively.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were determined on a Kofler hot stage and are uncorrected. Optical rotations were obtained for solutions in $CHCl_3$ (concentrations expressed in g/100 ml) on a Perkin-Elmer 241 polarimeter. Ir spectra were recorded on a Perkin-Elmer 1310 instrument. ^{1}H-nmr spectra were recorded at 100 MHz on a Varian XL-100-12 W6 spectrometer with internal TMS (δ scale). Thin layer chromatograms were carried out on Si gel G (Merck). The spots were visualized by spraying with HOAc-H_2SO_4-H_2O (80:4:16) and then heating at 110° for 3 min. Column chromatography was performed over Merck Kieselgel 60, particle size 0.063–0.200 mm. Elemental microanalysis was performed with a Heraeus, C,H, Mikrostandard type Analyser.

6β,11-DIACETOXYDRIM-7-ENE [**4**].—To a solution of **3** (0.5 g, 2.1 mmol) in dry pyridine (5 ml), was added Ac_2O (5 ml) and 4-dimethylaminopyridine (0.01 g). The mixture was stirred at room temperature for 48 h. A mixture of ice/H_2O was added, and the product was extracted with EtOAc. The organic phase was washed with HCl (5%), $NaHCO_3$ (5%), and H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed over SiO_2. Elution with hexane-EtOAc (80:20) gave 0.5 g of **4** (75%), as an oily product: ir (neat) 2980, 1740, 1240, 1020 cm^{-1}; ^{1}H nmr ($CDCl_3$) 0.96 (3H, s), 1.07 (3H, s), 1.09 (3H, s), 1.74 (3H, br s), 1.99 (3H, s, CO*Me*), 2.01 (3H, s, CO*Me*), 4.25 (2H, m, CH_2-OAc), 5.64 (m, 2H, H-6 and H-7). Found C 70.75, H 9.28; calcd for $C_{19}H_{30}O_4$, C 70.80, H 9.32.

6β,11-DIACETOXYDRIM-7-ENE-9α,12-DIOL [**5**].—To a solution of diacetate **4** (0.5 g, 1.6 mmol) in dry dioxane (20 ml) under N_2, was added a catalytic amount of selenium dioxide (0.01 g) and 1.2 g (3.9 mmol) of bis-(4-methoxyphenyl) selenoxide. The mixture was refluxed for 6 h. The solution was concentrated, and the residue was chromatographed over Si gel. Elution with petroleum ether-EtOAc (80:20) gave 0.25 g (46%) of the diol **5**: mp 142–143° (needles from hexane); ir (KBr) 3500, 3400, 1740, 1230, 1040 cm^{-1}; ^{1}H nmr ($CDCl_3$) 1.02 (3H, s), 1.12 (3H, s), 1.16 (3H, s), 2.05 (3H, s, CO*Me*), 2.12 (3H, s, CO*Me*), 2.48 (1H, br s, O*H*), 3.10 (1H, s, O*H*); (exchangeable with D_2O) 4.01–4.45 (4H, complex signal CH_2OH, CH_2-OAc); 5.64 (1H, dd, J = 4 and 5 Hz, H-6 OAc), 6.02 (1H, d, J = 5 Hz, H-7). Found C 64.30, H 8.50; calcd for $C_{19}H_{30}O_6$, C 64.41, H 8.47.

6β-ACETOXYDRIM-7-ENE-9α,11,12-TRIOL [**6**].—The diol **5** (0.24 g, 0.7 mmol) was stirred with a saturated solution of K_2CO_3 in MeOH (10 ml) for 0.5 h at room temperature. H_2O was added to the mixture, which was then extracted with CH_2Cl_2. After drying, the solvent was removed to give compound **6** (0.21 g, 98%): mp 115–116° (needles from heptane/CH_2Cl_2); $[\alpha]^{25}D$ −273.4 (c = 0.32, $CHCl_3$); ir 3400, 2980, 1730, 1240, 1020 cm^{-1}; ^{1}H nmr ($CDCl_3$) 1.00 (3H, s), 1.06 (3H, s), 1.12 (3H, s), 1.98 (1H, d, J = 4 Hz, H-5), 2.04 (3H, s, CO*Me*), 3.78 (2H, br s, 2 × H-11), [4.16 (J = 12, H-2) and 4.28 (J = Hz), AB system, 2 × H-12], 5.64 (1H, dd, J = 4 and 5 Hz, H-6-OAc), 5.94 (1H, d, J = 5 Hz, H-7). Found C 65.30, H 9.0; calcd for $C_{17}H_{28}O_5$, C 65.38, H 8.97.

(−)-6β-ACETOXY-9α-HYDROXYDRIM-7-ENE-11,12-DIAL (UGANDENSIDIAL) [**1**].—A mixture of CH_2Cl_2 (25 ml) and $(COCl)_2$ (0.120 ml, 1.28 mmol) was placed in a 25-ml three-neck round-bottom flask equipped with a mechanical stirrer, a thermometer, and two pressure equalizing dropping funnels containing DMSO (0.20 ml, 2.56 mmol) diluted with CH_2Cl_2 (1.5 ml) and the triol **6** (0.20 g, 0.64 mmol) in 2 ml of CH_2Cl_2. The DMSO was added to the stirred oxalyl chloride solution at −60°. The reaction mixture was stirred for 2 min, and the triol was added within 5 min. Stirring was continued for an additional 15 min, and triethylamine (0.8 ml, 5.8 mmol) was added. The reaction mixture was stirred for 5 min and then allowed to warm to room temperature. H_2O (10 ml) was added, and

the aqueous layer was reextracted with additional CH_2Cl_2 (50 ml). The organic layers were combined, washed with saturated NaCl solution, and dried. The solution was evaporated to dryness, and the residue was chromatographed over SiO_2. Elution with hexane/EtOAc gave 0.152 g (77%) of (−)-ugandensidial [**1**]: mp 140–141° (hexane CH_2Cl_2) [lit. (1) 141–143°], $[\alpha]^{25}D$ −412 (c = 0.64, $CHCl_3$) [lit. (1) $[\alpha]^{20}D$ −421 (c = 1.0, $CHCl_3$)]; ir 3420, 2940, 1740, 1720, 1680, 1200 cm^{-1}; ^1H nmr ($CDCl_3$) 1.02 (3H, s), 1.17 (3H, s), 1.34 (3H, s), 1.06 (1H, d, J = 4 Hz, H-5), 2.14 (3H, s, CO*Me*) 4.1 (1H, d, J = 1 Hz, O*H*), 5.92 (1H, dd, J = 4 and 5 Hz, H-6), 7.02 (1H, d, J = 5 Hz, H-7), 9.50 (1H, s, 12-CHO), 9.78 (1H, d, J = 1 Hz, 11-CHO). Found C 66.40, H 7.85; calcd for $C_{17}H_{24}O_5$, C 66.23, H 7.79.

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