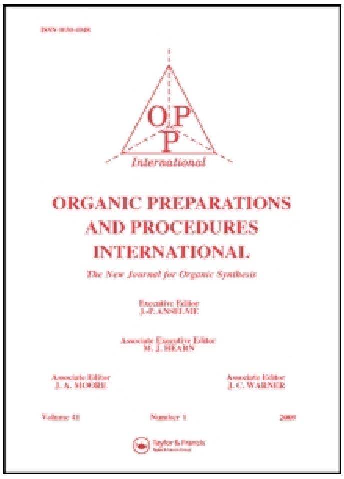

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SYNTHESIS OF (±)-EREMOFRULLANOLIDE

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SYNTHESIS OF (±)-EREMOFRULLANOLIDE

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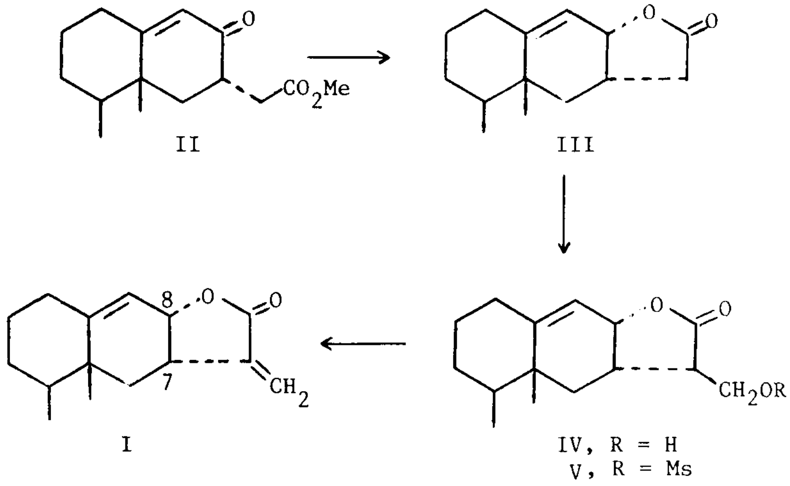
(+)-Eremofrullanolide I, which causes potent allergenic contact dermatitis, has recently been isolated from Frullania dilatata[1] by Asakawa and co-workers. The gross structure and stereochemistry of I were deduced from chemical and spectroscopic data. Recently we reported[2] a synthetic study relating to the synthesis of (±)-dugesialactone, a proposed double bond isomer of (±)-eremofrullanolide I. This study culminated in a revised structure for natural dugesialactone. In relation to this work, we were interested in verifying the stereochemistry depicted in (+)-eremofrullanolide I. Herein we report the first synthesis of (±)-eremofrullanolide.

Reaction of keto ester II[2] with L-Selectride in THF at -78° followed by acidification and subsequent chromatography gave the *cis*-lactone III (55%, mp. 105-107°). Irradiation of the vinyl proton in III caused the apparent triplet at δ4.96 to collapse to a doublet with $J_{7,8}$ = 5 Hz. The coupling constant is indicative of the assigned *cis* ring juncture stereochemistry in III. Reaction of lactone III with LDA at -78° followed by trapping the resulting enolate with gaseous formaldehyde[3] afforded the α-hydroxymethylene lactone IV (53%, mp. 128.5-130°). Treatment of IV with methanesulfonyl chloride in methylene chloride in the presence of triethylamine gave mesylate V (79%, mp. 131-132°). Re-



action of V with DBU in benzene at room temperature and subsequent chromatography afforded an 88% yield of (±)-eremofrullanolide I. The spectra of synthetic (±)-I were identical with those of natural (+)-eremofrullanolide I[4].

EXPERIMENTAL

The nmr spectra were recorded on a Bruker Model WM 250 and on a Varian Model EM 360 spectrometer at 250.13 and 60 MHz, respectively, (TMS as an internal standard). The high-resolution mass spectra data were obtained on a VG Micromass 70-70F spectrometer. Infrared spectra were determined on a Perkin-Elmer Model 727B spectrometer. The ratio of silica gel G to compound was approximately 12:1.

(3aξ,4aα,5α,9aβ)-3a,4,4a,5,6,7,8,8a,9a-Octahydro-4a,5-dimethylnaphtho-[2,3-b]-furan-2(3H)-one(III).- Keto ester II (2.06 g, 8.24 mmol) in 15 ml of dry THF was cooled to -78°. A THF solution of 1M L-Selectride (9.06 ml, 9.06 mmol) was added *via* a syringe over a 15 min period. The reaction mixture was stirred at -78° for 2 hrs.; methanol (8.0 ml) was then added and stirring was continued for 20 min. The reaction mixture was diluted with 40 ml of ether; 40 ml of 10% HCl was added and the resulting heterogeneous mixture was shaken for 20 min. The organic layer was separated and the aqueous solution was extracted with four 40 ml portions of ether. The combined organic solution was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*, giving an oil. Chromatography of the oil on silica gel G and elution with ether-hexane solutions gave 992 mg (55%) of III, mp. 105-107°; ^1H nmr (250 MHz, $CDCl_3$): δ 5.55 (d, 1H, J = 5 Hz), 4.69 (apparent t, 1H), 2.85 (dd, 1H, J = 17.1 and 7.8 Hz), 2.55 (m, 1H), 2.25 (d, 1H, J = 17.1 Hz), 0.97 (s, 3H) and 0.87 (d, 2H, J = 6.3 Hz); ir (KBr) 1776 cm^{-1}; irradiation of the vinyl proton at δ5.55 caused the apparent triplet at δ4.69 to collapse to a doublet at δ4.69, $J_{7,8}$ = 5 Hz; mass spectrum, calcd. for $C_{14}H_{20}O_2$ m/e 220.1463, found m/e 220.1462).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15

Found: C, 76.12; H, 9.28

(3α,3aβ,4aα,5α,9aβ)-3a,4,4a,5,6,7,8,8a,9a-Octahydro-4a,5-dimethyl-3-(hydroxymethyl)-naphtho[2,3-b]furan-2(3H)-one (VI).- Diisopropylamine (0.165 g, 1.63 mmol) in 2 ml of dry THF was cooled to 0°. A hexane solution of 2.1 M n-butyl lithium (0.78 ml, 1.63 mmol) was added *via* a syringe under N_2; the reaction mixture was stirred for an additional 20 min and then cooled to -78°. Lactone III (300 mg, 1.36 mmole) in 4 ml of THF was added *via* a syringe over a 20 min period and stirring was continued at -78° for an additional 20 min. The reaction mixture was allowed to warm to -20° and was stirred at -20° for 20 min. Gaseous formaldehyde, generated from paraformaldehyde [(1.5 g) at 150°], was passed into the reaction mixture via a N_2 stream over a 2 hr. period. The reaction mixture was diluted with 40 ml of ethyl acetate and extracted with 40 ml of brine. The aqueous solution was extracted with four 25 ml portions of ethyl acetate. The combined organic solution was washed with brine, dried ($MgSO_4$) and concentrated in vacuo, giving an oil. Chromatography of the oil on silica gel G and elution with ether-hexane solutions afforded 180 mg, (53%) of IV, mp. 128.5-130°; ^1H nmr (250 MHz, $CDCl_3$): δ 5.53 (d, 1H, J = 4.4 Hz), 4.84 (apparent t, 1H), 3.98 (m, 2H), 0.97 (s, 3H) and 0.88 (d, 3H, J = 5.9 Hz); ir (KBr) 3390 and 1740 cm^{-1}; mass spectrum, calcd. for $C_{15}H_{22}O_3$ m/e 250.1568, found m/e 250.1588).

(3α,3aβ,4aα,5α,9aβ)-3a,4,4a,5,6,7,8,8a,9a-Octahydro-4a,5-dimethyl-3-[((methylsulfonyl)oxy)methyl]naphtho[2,3-b]furan-2(3H)-one(V).- Dry triethylamine (87.14 mg, 0.12 ml, 0.863 mmol) was added via a syringe to alcohol IV (180 mg, 0.719 mmol) in 3 ml of dry CH_2Cl_2 at -5° to -10° under N_2. Methanesulfonyl chloride (0.061 ml, 90.6 mg, 0.791 mmol) was added dropwise via a syringe over a 10 min period. The reaction mixture was stirred between 0° and -10° for 3.5 hrs., diluted with 100 ml of CH_2Cl_2, and washed with 15 ml of ice-cold water, 15 ml of 10% HCl, 15 ml of 10% $NaHCO_3$ and 15 ml of brine. The organic solution was dried ($MgSO_4$) and concentrated in vacuo to afford 205 mg of a solid. Trituration of the solid with an ether-hexane solution gave 186 mg, (79%) of V, mp. 131-132°; ^1H (nmr, 60 MHz, $CDCl_3$): δ 5.53 (d, 1H), 4.83 (m, 1H, CHOCO, unresolved), 4.50 (d, 2H) and 3.04 (s, 3H); ir (KBr) 1780, 1352, and 1180 cm^{-1}. The mesylate was not characterized further, but submitted directly to the elimination reaction.

(±)-Eremofrullanolide(I).- DBU (89.1 mg, 0.0875 ml, 0.585 mmol) was added via a syringe, over a 10 min period to mesylate V (160 mg, 0.488 mmol) in 4 ml of dry benzene under N_2 at room temperature with stirring. The reaction mixture was stirred for 3.5 hrs. and then diluted with 150 ml of ethyl acetate. The organic solution was washed with 10 ml of cold water, 15 ml of 10% HCl and 15 ml of cold water, dried ($MgSO_4$) and concentrated *in vacuo* to afford a solid. Chromatography of the solid on silica gel G and elution with ether-hexane solutions afforded (100 mg, 88%) of (±)-eremofrullanolide I, mp. 88-88.5°; lit.[1] mp. of(+)-eremofrullanolide 82-82.5°; ^{1}H nmr (250 MHz, $CDCl_3$): δ 6.19 (d, 1H, J = ~1Hz), 5.62 (d, 1H, J = ~1 Hz), 5.88 (d, 1H, J = 4.6 Hz), δ 4.66 (apparent t, 1H), 3.02-3.12 (m, 1H), 2.20-2.25 (m, 2H), 1.80 (dd, J = 13.4 and 5.3 Hz) and 1.71-1.79 (m) [2H], 1.55 - 1.78 (m, 5H), 1.0 (s, 3H) and 0.88 (d, 3H, J = 6.3 Hz); irradiation of the vinyl proton at δ 5.88 caused the apparent triplet at δ4.66 to collapse to a doublet at 4.66 ($J_{7,8}$ = 5.9 Hz); ir (KBr) 1770 cm^{-1}; mass spectrum, calcd. for $C_{15}H_{20}O_2$ m/e 232.1463, found m/e 232.1463).

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