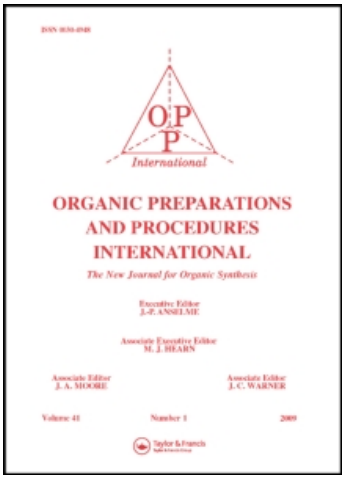

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AN IMPROVED PREPARATION OF A TRICYCLIC LACTONE, A POTENTIALLY USEFUL PRECURSOR OF HIGHLY FUNCTIONALIZED TERPENOIDS

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6. Reactants and solvents were commercially available, reagent grade.

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Submitted by (11/19/90) J. Zinczuk, J. A. Bacigaluppo, M. P. Mischne, M. I. Colombo and E. A. Rúveda*

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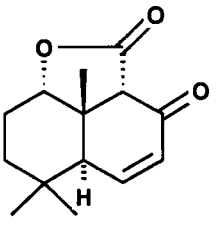
The tricyclic lactone **1** was found to be a valuable intermediate for the synthesis of the biologically important and highly oxygenated labdane diterpene forskolin **2**[1] and some 1-hydroxy-drimanes related to the sesquiterpene warburganal **3**.[2] The synthesis (and spectroscopic properties) of **1** *via* an intramolecular Michael addition (**4** → **5**) in tandem with an intramolecular aldol condensation (**5** → **1**), was reported almost simultaneously by Wu et al.[3] and by us.[4]



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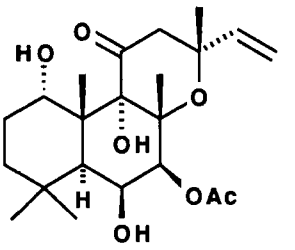

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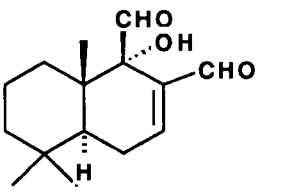
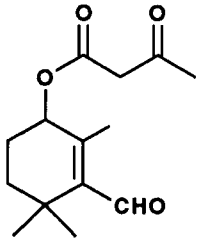


3

In spite of the simplicity of the sequence, reproducible yields are obtained only if our experimental conditions are followed carefully. For example, the purity of β-keto ester **4** is crucial and column chromatography is necessary to separate the bicyclic lactone **5** from the hemiacetal **6**, also formed in the reaction. Furthermore, the reaction time of the acid-catalyzed aldol condensation of **5** has to be carefully monitored by ^{1}H NMR spectroscopy, in order to avoid the formation of appreciable amounts



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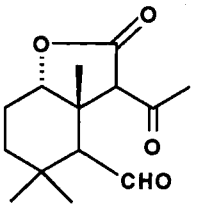

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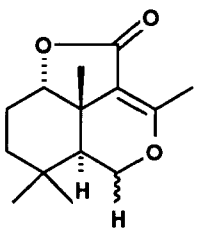

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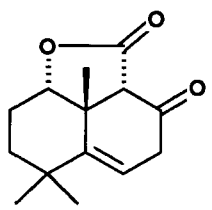

7

of the more stable β,γ-unsaturated ketone **7**, before the total consumption of the starting material. Since **1** is potentially useful for the synthesis of other polyoxygenated terpenoids, it was of interest to study its preparation in detail in order to have a more practical access to this attractive starting material.

Treatment of the crude β-keto ester **4**[4] with potassium tert-butoxide in refluxing benzene for 3 hrs. afforded **5** in 60-66% yield, after purification of the crude reaction product by washing with diethyl ether. Under these conditions, the formation of **6** was not detected by thin layer chromatography. The acid-catalyzed aldol condensation step was carried out by refluxing a dilute solution of **5** and an equimolecular amount of p-toluenesulfonic acid monohydrate in 1,2-dichloroethane for approximately 5 hrs. Flash chromatography on silica gel of the crude reaction product afforded **1** in 80-82% yield. The use of 1,2-dichloroethane instead of benzene allow better control of the reaction time; under these conditions, the starting material **5** was nearly completely consumed and the formation of **7** was negligible. The reaction can be monitored by thin layer chromatography.

EXPERIMENTAL SECTION

Mps were determined on a hot-stage microscope and are uncorrected. IR spectra were measured as KBr disks. The ^{1}H NMR spectra were recorded at 80 MHz in $CDCl_3$ solutions and the ^{13}C NMR spectra were measured at 20.15 MHz. Column chromatography was performed on silica gel 60 H, slurry packed, run under low pressure of nitrogen and employing increasing amounts of ethyl acetate in hexane as solvent. Analytical thin-layer chromatography (TLC) was conducted on Merck aluminum plates precoated with 0.2 mm of silica gel 60F-254.

(2aβ,5aα,8aβ,8bβ)-2a,3,5a,6,7,8,8a,8b-Octahydro-3-oxo-6,6,8b-trimethyl-2H-naphtho[1,8-bc]furan-2-one (**1**).- To a stirred solution of freshly sublimed potassium tert-butoxide[5] (4.032 g, 36 mmol) in anhydrous benzene (250 ml) under nitrogen at room temperature was added dropwise (5 min) a solution of crude **4** (7.56 g, 30 mmol)[4] in anhydrous benzene (50 ml). The resulting orange

suspension was heated at reflux for 3 hrs until the TLC spot for the starting material had disappeared. The cooled reaction mixture was then poured into ice-cooled 0.5N hydrochloric acid (100 ml) and the aqueous layer was extracted further with benzene (50 ml x 2). The combined organic extracts were washed with water, brine, dried ($MgSO_4$) and evaporated. The yellow oily residue (approximately 6 g) was then triturated with diethyl ether and cooled at -15° twice to give **5** as a crystalline mass (4.5-5 g, 60-66%), mp. 95-98°, lit.[3] 93-95°. IR, ^1H and ^{13}C NMR spectra coincided with those previously reported.[4]

To a stirred solution of p-toluenesulfonic acid monohydrate (950 mg, 5 mmol) in freshly distilled 1,2-dichloroethane (500 ml) under nitrogen at room temperature, was added dropwise (10-15 min) a solution of **5** (1.26 g, 5 mmol) in 1,2-dichloroethane (200 ml) dropwise. The yellowish solution was heated at reflux for 5 hrs until TLC spot for the starting material had disappeared. If heating was continued for a longer period, the quantitative transformation into **7** was observed. The cooled solution was washed with water (2 x 100 ml) and brine (100 ml), dried ($MgSO_4$) and evaporated. Flash chromatography of the yellow solid residue (2.15 g) on silica gel 60H, employing increasing amounts of ethyl acetate in hexane as solvent, resulted in the isolation of pure **1** (0.94-0.96 g, 80-82%), mp. 149-151°, lit.[3,4] 152-153°, 152.5-154°. IR, ^1H and ^{13}C NMR spectra coincided with those previously reported.[4]

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