J. Braz. Chem. Soc., Vol. 10, No. 2, 112-116, 1999.
Printed in Brazil.

0103 – 5053 $6.00 + 0.00

Article

A Novel Synthesis of 1-Acetyl-4-Isopropenyl-1-Cyclopentene by Chemoselective Cyclization of 4-Methyl-3-(Oxobutyl)-4-Pentenal: An Important Intermediate for Natural Product Synthesis

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Neste artigo apresentamos a oxidação direta do epóxi-limoneno **1** com KIO_4 em água como uma melhor alternativa para se obter o ceto-aldeído **3**, um importante intermediário na síntese de produtos naturais. O ceto-aldeído **3** é ciclizado com Al_2O_3-ácido de forma quimosseletiva produzindo, preferencialmente, a cetona **4**. Estas duas reações elevam o rendimento total da síntese da cetona **4** para 70% em comparação com 8% pelo método citado na literatura[1].

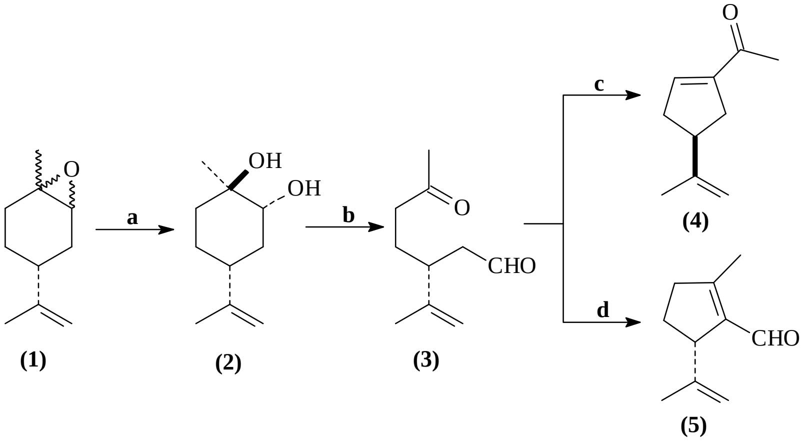
This article presents the direct oxidation of limonene-oxide **1** with KIO_4 in water, which is the best way to obtain the keto-aldehyde **3**, an important intermediate in natural product synthesis. The cyclization of keto-aldehyde **3** with acidic Al_2O_3 proceeds chemoselectively to give ketone **4**. These two reactions together increase the overall yield of ketone **4** to about 70% compared to 8% previously reported in the literature[1].

Keywords: *terpenoid chirons, epoxide ring opening, KIO_4 oxidation, chemoselective cyclization*

Introduction

Terpenes are abundant chiral compounds present in nature and an important source of intermediaries for natural product synthesis[2-3].

Wolinsky by two routes[4-5] prepared ketone **4** (Fig. 2), a natural product first isolated from Spanish *Eucalyptus globulus* in 1947[5] and aldehyde **5** (Fig. 4), an important intermediate in several natural product syntheses[6-11](Fig. 1), from limonene-oxide **1** (Scheme 1). The keto-aldehyde **3**, intermediate in the Wolinsky approach has also been used in the study of asymmetric cyclizations[12] and chemoselective reduction[13].



Scheme 1. a) 1% H_2SO_4 / H_2O, 0-5 °C, 1 h, 39% (**2**); b) $NaIO_4$ / H_2O, r.t., 3 days; c) 10% KOH / H_2O, r.t., 19% from diol (**2**); d) piperidine / AcOH / benzene, reflux, 1 h, 59% (5).

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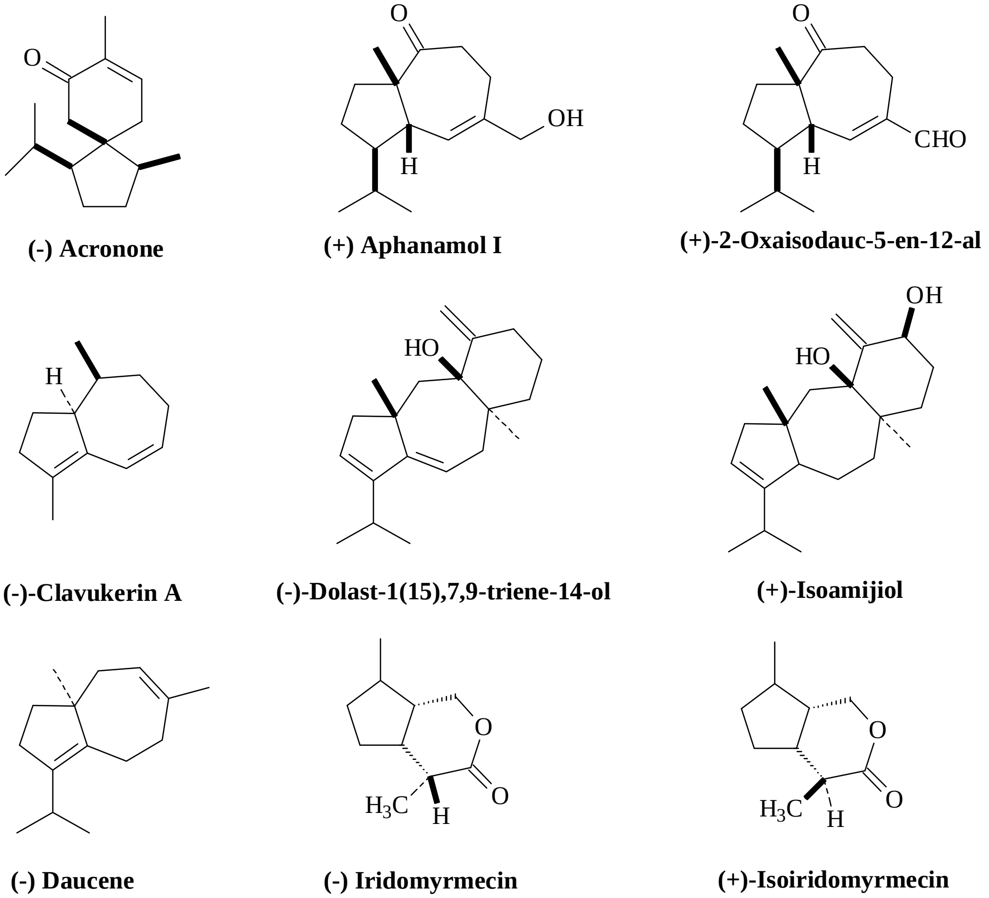
Only two other papers reported the formation of ketone **4**: First, in 1977, Wolinsky[14] reported the formation of ketone **4** from α-Pinene (Fig. 2) and then, in 1996, Jones and Kover[15] demonstrated the formation of the enantiomer of ketone **4** by hydrolysis of epoxy-tosylates prepared from (-)-R-Carvone (Fig. 3), but the first Wolinsky synthesis still remained the route of choice to prepare the ketone **4**.

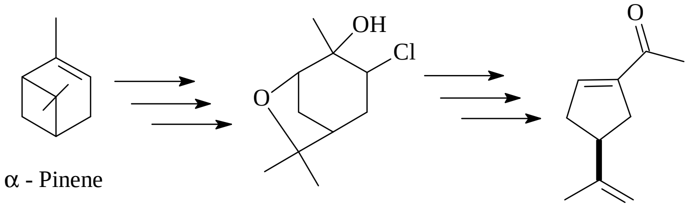


(-) Acronone **(+) Aphanamol I** **(+)-2-Oxaisodauc-5-en-12-al**

(-)-Clavukerin A **(-)-Dolast-1(15),7,9-triene-14-ol** **(+)-Isoamijiol**

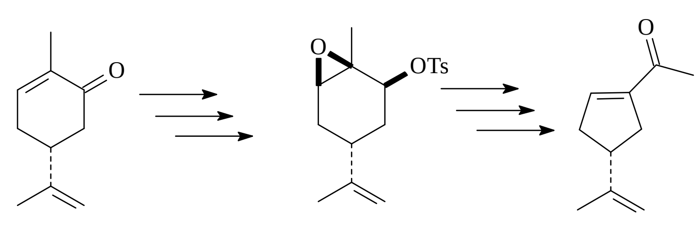
(-) Daucene **(-) Iridomyrmecin** **(+)-Isoiridomyrmecin**

Figure 1. All the compounds above have been prepared from keto-aldehyde **3**.



(4)

Figure 2.



(4a)

Figure 3.

In the original Wolinsky approach which gave a low overall yield for formation of ketone **4**, the diol **2** was obtained in 39% yield and the subsequent cyclization of keto-aldehyde **3**, proceeded in only 10% yield.

Diol **2** is soluble in water, and thus the reaction is best conducted at low temperature and with occasional shaking to induce the formation of crystals. The isolation of diol **2**, as an oil, from water is difficult. Diol **2** is also obtained in its hydrated which complicates its characterization and quantification. Drying the diol adds a tedious but necessary task to the whole process in order to avoid use of excess $NaIO_4$[13], even though the periodate cleavage is conducted in aqueous medium.

The cyclization of keto-aldehyde **3** leads to a mixture of ketone **4** and aldehyde **5**, which is very difficult to separate by conventional methods. Attempts to purify **4** by distillation led to substantial losses of material even under reduced pressure. Preparative chromatography was not an alternative since **4** and **5** elute together in all solvent mixtures tested. The chemoselective preparation of aldehyde **5**[16], *via* formation of an enamine (Fig. 4), was reported in the literature[4], but a chemoseletive preparation for ketone **4** was still necessary[17].

Discussion and Results

We wish to report here two modifications of Wolinsky's approach that solve the problems outlined above and enhance the yields of keto-aldehyde **3** and the ketone **4**[17].

First we oxidized limonene-oxide **1** directly with KIO_4 leading to keto-aldehyde **3** in one step and high yield (85%). This avoids preparation of intermediate diol **2**, represents economy of time and reagent and solves the problems associated with isolation of diol **2**. Although oxidation of epoxides with HIO_4 was reported in the literature[18], it has never been applied to limonene-oxide **1**.

Second, continuing our study of cyclization of 1,6 dicarbonyls we cyclized keto-aldehyde **3** with acidic Al_2O_3 [19] and verified that the process was highly chemoselective resulting in ketone **4** in high yield (95%).

(+)-R-limonene **7** was initially epoxidized with peracid prepared *in situ* by mixing ethyl chloroformate and H_2O_2 in dichloromethane (Scheme 2). The desired limonene-oxide **1** was isolated by distillation, as a mixture of dias-

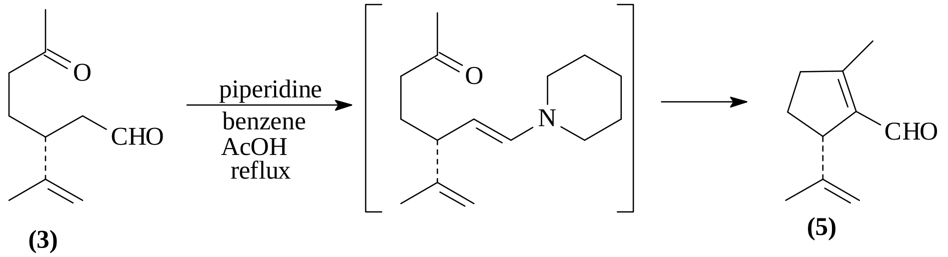
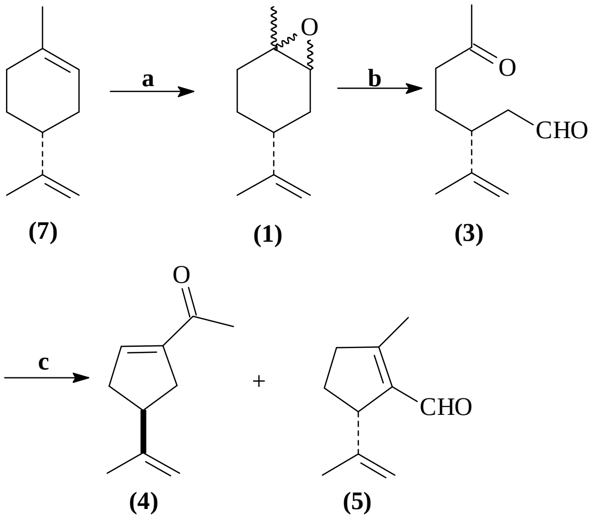


Figure 4.



8 : 1 by HRGC
14 : 1 by ^{1}H NMR

Scheme 2. a) 30% H_2O_2, ethyl chloroformate, $NaHPO_4$, CH_2Cl_2, r.t., 48 h, 73% (**1**); b) KIO_4 (1 eq), H_2O, 55 °C, 8 h, 85% (**3**); c) Al_2O_3 - acid, hexane, reflux, 65 °C, 7 h, 95% (**4**).

tereomers, in 73% yield. This mixture of epoxides was then treated with an equimolar quantity of KIO_4 in water.

We observed the formation of at least three side products (by HRGC analysis) during the oxidation of limonene-oxide **1** with KIO_4. They were not characterized but could be ascribed to epoxide ring opening products from attack of various nucleophiles present in the reaction medium. Keto-aldehyde **3** was refluxed in hexane over acidic Al_2O_3 while the reaction was monitored by HRGC. Analysis of the product mixture after the total consumption of keto-aldehyde **3** shows a ketone **4** to aldehyde **5** ratio of 4:1 (by integration of peak area). When the reaction was conducted at reflux for prolonged times the ratio of **4** to **5** increased to 8:1 (HRGC) After isolation, analysis of the crude light yellow oil revealed a ratio of **4** to **5** of 14:1. This ratio was determined by comparison of the integrated ^{1}H-NMR signal of the aldehyde proton present in compound **5** (δ 9.95 ppm), and the vinylic proton present in compound **4** (δ 6.68 ppm).

It is not clear if chemoselectivity arises from a simple equilibration of products due to catalysis on the surface of the alumina or if the selectivity arises during the desorption from alumina[20].

Conclusion

Ketone **4** was prepared efficiently, selectively, and in high overall yield by comparison with previous routes. Cyclization of aldehyde **3** with acidic Al_2O_3 is shown to be very chemoselective. The direct oxidation of epoxy-limonene **1** with KIO_4 is a novel and better way to obtain keto-aldehyde **3**, an important intermediate for natural product synthesis.

Experimental

General

(+)-R-Limonene was distilled prior to use. Solvents and inorganic reagents were used without further purification. Analyses by HRGC were performed on a HP-5890-II gas chromatograph with fid by using a 30 m (length), 0.25 mm (ID) and 25 μm (phase thickness) RTX-5 silica capillary column and H_2 (flow rate 50 cm s^{-1}) as carrier gas (split 1:20). Oven temp.: 70 °C then 10 °C / min to 280 °C (2 min), injector temp.: 200 °C, detector temp.: 280 °C. Mass spectra were obtained on a Hewlett-Packard HP-5896-A HRGC-MS using electron impact (70 ev). ^{1}H-NMR and ^{13}C-NMR were acquired on a Bruker DRX-300 (300 MHz and 75 MHz, respectively) spectrometer for $CDCl_3$ solutions with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin Elmer 1600 FT-IR or on a Nicolet 740 FT-IR spectrometers (NaCl film).

Limonene-oxide **(1)**

To a 1 liter round-bottom flask equipped with a magnetic stirrer were added 25 g (180 mmol) of (R)-(+) limonene, 29 mL (180 mmol) of ethyl chloroformate, 193 mL of 30% H_2O_2, 193 mL of dichloromethane and 178 g of $NaHPO_4$. The flask and contents were vigorously stirred at room temperature for 48 h (limonene consumption was followed by gas chromatography). Upon consumption of starting material the mixture was separated in a separatory funnel. The aqueous phase was extracted with dichloromethane (3 x 50 mL). The combined organic phases were washed with 1% aqueous sodium sulfite solution until complete decomposition of excess H_2O_2. The presence of H_2O_2 was verified with a standard starch-I_2 test. The organic phase was then washed with water (3 x 75 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated in a rotatory evaporator. The resulting oil was distilled under reduced pressure (3 mmHg) and a fraction corresponding to compound **1** was collected at 40 °C (20 g, 131.5 mmol, 73% yield). The identity of this fraction was confirmed by analysis by GC/MS and IR, and by comparison to an authentic sample.

4-Methyl-3-(oxobutyl)-4-pentenal **(3)**

A 250 mL round-bottom flask equipped with a magnetic stirrer was charged with 13 g (85 mmol) of 1,2-limonene oxide (**1**), followed by addition of a suspension of 19.6 g (85 mmol) of KIO_4 in 200 mL of water. The flask and contents were heated on a steam bath to 55 °C and vigorously stirred for 8 h. The limonene-oxide consumption was followed by gas chromatography. Upon consumption of starting material the mixture was saturated with NaCl and was extracted with ether (3 x 60 mL). The layers were separated and the organic phase was dried over anhydrous Na_2SO_4. The solvent was evaporated in a rotatory evaporator at room temperature. Compound **3** was isolated as an oil (obtained 12 g, 71.4 mmol, 85% yield) that was pure enough to use in the next reaction. This oil was analyzed by GC/MS, IR, ^{1}H and ^{13}C-NMR, and then it was compared with an authentic sample.

^{1}H-NMR δ (ppm): 1.37-1.60 (m, 2H), 1.46 (s, 3H), 1.95 (s, 3H), 2.3-2.3 (m, 4H), 2.50-2.55 (m, 1H), 4.6(d, 2H), 9.4 (s, 1H). ^{13}C-NMR δ (ppm): 18.5, 26.2, 29.7, 40.5, 40.6, 47.1, 112, 145, 201, 208. IR (neat) ν (cm^{-1}) 3050, 2920, 2710, 1710, 1630, 1430, 1360, 1160, 890, 730. MS (%) m/z 150(10), 135(10), 107(30), 67(30), 43(100), (molecular ion m/z 168, not found).

1-Acetyl-4-isopropenyl-1-cyclopentene **(4)**

To a 500 mL round-bottom flask equipped with a magnetic stirrer and a reflux condenser were added 12 g (71 mmol) of aldehyde **3**, 300 mL of hexane and 50 g of acidic Al_2O_3. The flask and contents were heated on a steam bath to 65 °C with vigorous agitation. Aldehyde consumption was accompanied by gas chromatography. Upon consumption of starting material the mixture was filtered in a Buchner funnel and washed with $CHCl_3$ (4 x 50 mL). The organic solution was dried over anhydrous Na_2SO_4 and the solvent was evaporated in a rotatory evaporator at room temperature. Compound **4** was obtained as an oil (10.5 g, 70 mmol, 90% pure by HRGC, 95% yield). This oil was analyzed by GC/MS, IR, ^{1}H and ^{13}C-NMR, and then compared with an authentic sample.

^{1}H-NMR δ (ppm): 1.7 (s, 3H), 2.29 (s, 3H), 2.35-2.52 (m, 2H), 2.65-2.78 (m, 2H), 2.9-3.1 (m, 1H), 4.18 (d, 2H), 6.68 (s, 1H) ^{13}C NMR δ (ppm): 20.5, 26.5, 35.3, 38.6, 44.8, 109.4, 143.4, 145.2, 147.4, 196.8. IR (neat) ν (cm^{-1}) 3050, 2940, 1665, 1606, 1403, 1390, 1260, 870, 810. MS (%) m/z 150 (M$^+$ 60), 135 (80), 107 (50), 91 (60), 65 (20), 43 (100).

Acknowledgments

We thank the CNPq and PADCT for financial support, Prof. C.R. Kaiser and C.P.S Chaves for ^{1}H and ^{13}C-NMR spectrometry and R.M.A. Bento for mass spectrometry.

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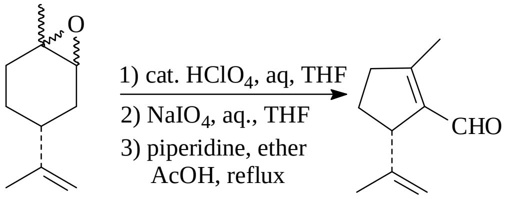

(5)

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Received: May 22, 1998