

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

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Neste artigo apresentamos a oxidação direta do epóxi-limoneno **1** com KIO<sub>4</sub> 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<sub>2</sub>O<sub>3</sub>-ácido de forma quimoseletiva 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<sup>1</sup>.

This article presents the direct oxidation of limonene-oxide **1** with KIO<sub>4</sub> 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<sub>2</sub>O<sub>3</sub> 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<sup>1</sup>.

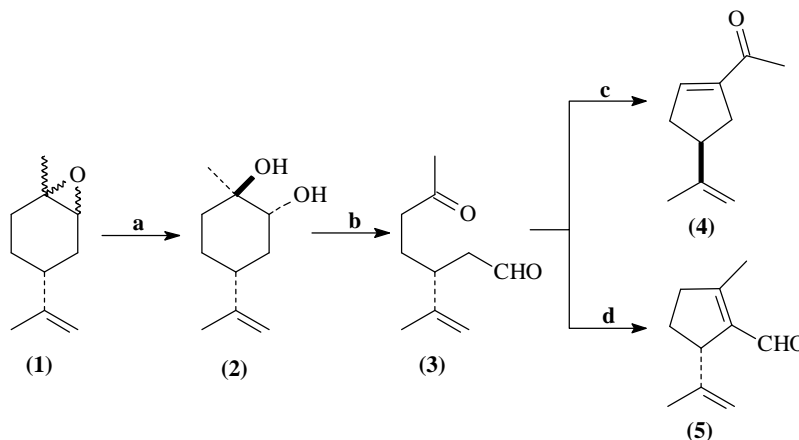
**Keywords:** *terpenoid chirons, epoxide ring opening, KIO<sub>4</sub> oxidation, chemoselective cyclization*

### Introduction

Terpenes are abundant chiral compounds present in nature and an important source of intermediaries for natural product synthesis<sup>2-3</sup>.

Wolinsky by two routes<sup>4-5</sup> prepared ketone **4** (Fig. 2), a natural product first isolated from Spanish *Eucalyptus*

*globulus* in 1947<sup>5</sup> and aldehyde **5** (Fig. 4), an important intermediate in several natural product syntheses<sup>6-11</sup>(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<sup>12</sup> and chemoselective reduction<sup>13</sup>.



**Scheme 1.** a) 1% H<sub>2</sub>SO<sub>4</sub> / H<sub>2</sub>O, 0-5 °C, 1 h, 39% (2); b) NaIO<sub>4</sub> / H<sub>2</sub>O, r.t., 3 days; c) 10% KOH / H<sub>2</sub>O, r.t., 19% from diol (2); d) piperidine / AcOH / benzene, reflux, 1 h, 59% (5).

Only two other papers reported the formation of ketone **4**: First, in 1977, Wolinsky<sup>14</sup> reported the formation of ketone **4** from  $\alpha$ -Pinene (Fig. 2) and then, in 1996, Jones and Kover<sup>15</sup> 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**.

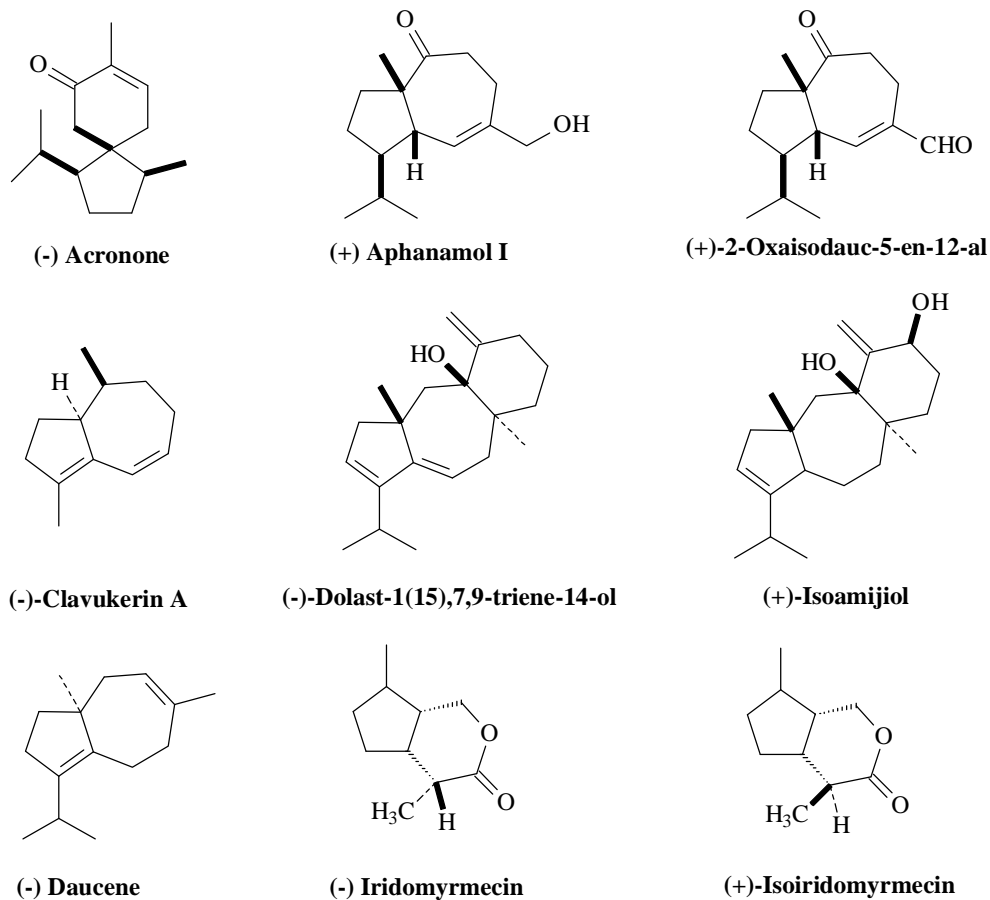


Figure 1. All the compounds above have been prepared from keto-aldehyde **3**.

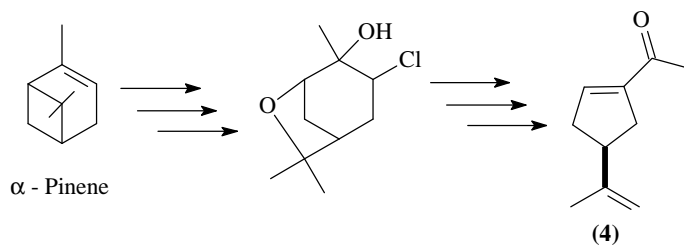


Figure 2.

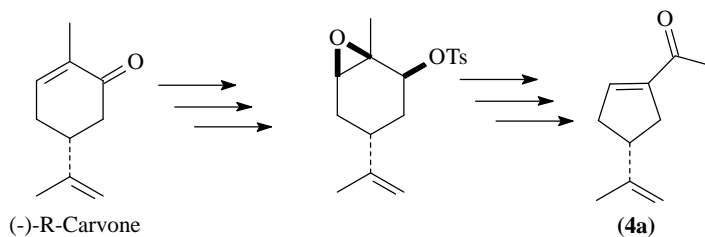


Figure 3.

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  $\text{NaIO}_4$ <sup>13</sup>, 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**<sup>16</sup>, *via* formation of an enamine (Fig. 4), was reported in

the literature<sup>4</sup>, but a chemoselective preparation for ketone **4** was still necessary<sup>17</sup>.

## 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**<sup>17</sup>.

First we oxidized limonene-oxide **1** directly with  $\text{KIO}_4$  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  $\text{HIO}_4$  was reported in the literature<sup>18</sup>, 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  $\text{Al}_2\text{O}_3$ <sup>19</sup> 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  $\text{H}_2\text{O}_2$  in dichloromethane (Scheme 2). The desired limonene-oxide **1** was isolated by distillation, as a mixture of dias-

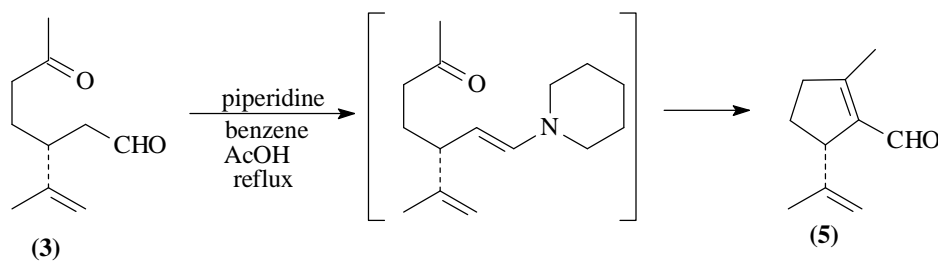
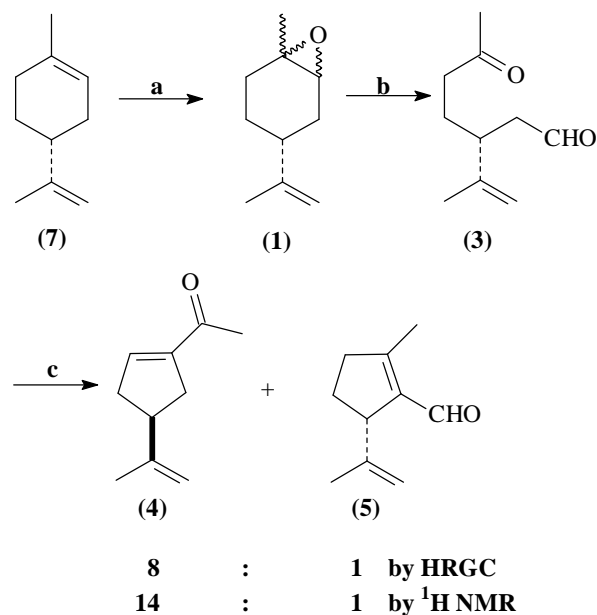


Figure 4.



**Scheme 2.** a) 30%  $\text{H}_2\text{O}_2$ , ethyl chloroformate,  $\text{NaHPO}_4$ ,  $\text{CH}_2\text{Cl}_2$ , r.t., 48 h, 73% (**1**); b)  $\text{KIO}_4$  (1 eq),  $\text{H}_2\text{O}$ , 55 °C, 8 h, 85% (**3**); c)  $\text{Al}_2\text{O}_3$  - 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  $\text{KIO}_4$  in water.

We observed the formation of at least three side products (by HRGC analysis) during the oxidation of limonene-oxide **1** with  $\text{KIO}_4$ . 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  $\text{Al}_2\text{O}_3$  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  $^1\text{H-NMR}$  signal of the aldehyde proton present in compound **5** ( $\delta$  9.95 ppm), and the vinylic proton present in compound **4** ( $\delta$  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<sup>20</sup>.

## Conclusion

Ketone **4** was prepared efficiently, selectively, and in high overall yield by comparison with previous routes. Cyclization of aldehyde **3** with acidic  $\text{Al}_2\text{O}_3$  is shown to be very chemoselective. The direct oxidation of epoxy-limonene **1** with  $\text{KIO}_4$  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  $\mu\text{m}$  (phase thickness) RTX-5 silica capillary column and  $\text{H}_2$  (flow rate 50  $\text{cm s}^{-1}$ ) as carrier gas (split 1:20). Oven temp.: 70  $^\circ\text{C}$  then 10  $^\circ\text{C} / \text{min}$  to 280  $^\circ\text{C}$  (2 min), injector temp.: 200  $^\circ\text{C}$ , detector temp.: 280  $^\circ\text{C}$ . Mass spectra were obtained on a Hewlett-Packard HP-5896-A HRGC-MS using electron impact (70 eV).  $^1\text{H-NMR}$  and  $^{13}\text{C-NMR}$  were acquired on a Bruker DRX-300 (300 MHz and 75 MHz, respectively) spectrometer for  $\text{CDCl}_3$  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%  $\text{H}_2\text{O}_2$ , 193 mL of dichloromethane and 178 g of  $\text{NaHPO}_4$ . 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  $\text{H}_2\text{O}_2$ . The presence of  $\text{H}_2\text{O}_2$  was verified with a standard starch- $\text{I}_2$  test. The organic phase was then washed with water (3 x 75 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , 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  $^\circ\text{C}$  (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  $\text{KIO}_4$  in 200 mL of water. The flask and contents were heated on a steam bath to 55  $^\circ\text{C}$  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  $\text{Na}_2\text{SO}_4$ . 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,  $^1\text{H}$  and  $^{13}\text{C-NMR}$ , and then it was compared with an authentic sample.

$^1\text{H-NMR}$   $\delta$  (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).  $^{13}\text{C-NMR}$   $\delta$  (ppm): 18.5, 26.2, 29.7, 40.5, 40.6, 47.1, 112, 145, 201, 208. IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 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  $\text{Al}_2\text{O}_3$ . 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  $\text{CHCl}_3$  (4 x 50 mL). The organic solution was dried over anhydrous  $\text{Na}_2\text{SO}_4$  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,  $^1\text{H}$  and  $^{13}\text{C}$ -NMR, and then compared with an authentic sample.

$^1\text{H}$ -NMR  $\delta$  (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)  $^{13}\text{C}$  NMR  $\delta$  (ppm): 20.5, 26.5, 35.3, 38.6, 44.8, 109.4, 143.4, 145.2, 147.4, 196.8. IR (neat)  $\nu$  ( $\text{cm}^{-1}$ ) 3050, 2940, 1665, 1606, 1403, 1390, 1260, 870, 810. MS (%)  $m/z$  150 ( $\text{M}^+$  60), 135 (80), 107 (50), 91 (60), 65 (20), 43 (100).

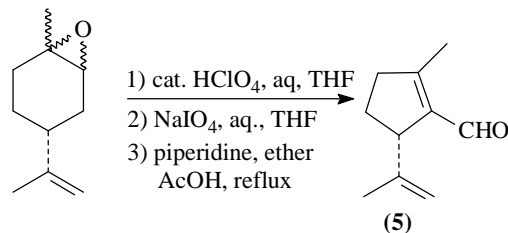
### Acknowledgments

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