

Article

## Asymmetric Synthesis of 6-Carbomethoxyethyl-6-Methyl- $\epsilon$ -Caprolactone

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Uma síntese assimétrica eficiente e curta de ambos os enantiômeros **1** e *ent-1* foi efetuada em 90% e.e. por meio da oxidação de Baeyer-Villiger de cicloexanonas quirais  $\alpha,\alpha$ -disubstituídas. Um painel sensorial descreveu **1** como possuindo um aroma agradável de amêndoas, enquanto *ent-1* possui um leve aroma de rosas.

A short and efficient asymmetric synthesis of both enantiomers **1** and *ent-1* has been performed in 90% e.e. by means of Baeyer-Villiger oxidation from chiral  $\alpha,\alpha$ -disubstituted cyclohexanones. An expert aroma panel has identified **1** as having a pleasant almond-like aroma odor, while *ent-1* has a weak floral odor.

**Keywords:** *flavor, asymmetric synthesis, lactones*

### Introduction

Flavors and fragrances are complex mixtures of volatile compounds and generally consist of hundreds of substances with different functionalities<sup>1</sup>. Among them, lactones are known for their unique organoleptic properties as evidenced by early descriptions by chemists as compounds having lactone-like odor properties<sup>2,3</sup>. The relationship between chirality and odor quality is an important aspect to flavor chemistry which has been actively investigated in recent years. Indeed, chiral 4-substituted- $\gamma$ -butyrolactones and 5-substituted- $\gamma$ -valerolactones have attracted substantial attention because of their importance as flavor components<sup>3-5</sup>. In the same way, some 4,4-disubstituted- $\gamma$ -butyrolactones have been reported as tobacco constituents<sup>6</sup> and 4,4-dibutyl- $\gamma$ -butyrolactone as a coconut-like flavor<sup>3</sup>. On the other hand, to the best of our knowledge, no examples are available on sensory properties of different enantiomers of chiral 6,6-disubstituted- $\epsilon$ -caprolactones.

### Results and Discussion

Herein we report the asymmetric syntheses<sup>7</sup> and the sensory properties of both enantiomers of 6-carbomethoxyethyl-6-methyl- $\epsilon$ -caprolactone, **1** and *ent-1*, which were prepared from 2-methylcyclohexanone **2**

(Scheme 1). Compound **2** was converted into chiral  $\alpha,\alpha$ -disubstituted ketone **3** by using the asymmetric Michael addition reaction to introduce the chiral center in **3**<sup>8</sup>. Treatment of **2** with S(-)-phenylethylamine led to the corresponding chiral imine which was *in situ* allowed to react with methyl acrylate affording the ketoester **3** in a 81% yield and 90% e.e., as described in the literature<sup>9</sup>. The expansion of the six-membered ring of **3** was achieved by Baeyer-Villiger oxidation<sup>10</sup>. Thus, treatment of **3** with MCPBA (1.0 eq.) at reflux for 6 h under an argon atmosphere in the presence of lithium carbonate in CH<sub>2</sub>Cl<sub>2</sub> furnished, after work up, the caprolactone **1** as a pale yellow liquid in a 65% yield and 90% e.e., with configuration being retained at the chiral center<sup>11</sup>. Compound *ent-1* was obtained also as yellow liquid in identical chemical yield and optical purity from **2** by employing R(+)-1-phenylethylamine as the chiral auxiliary in the same synthetic protocol described above.

The caprolactones **1** and *ent-1* readily prepared from **3** and *ent-3*, respectively, were distilled by using a vacuum-jacketed column. Next, in both cases, only one peak was observed by HRGC analysis by using an HP-1 (12 m x 0.2 mm x 0.33  $\mu$ m) column, suggesting they were obtained in high chemical purities.

Optical purities (e.e.) of caprolactones **1** and *ent*-**1** were directly determined by using  $^1\text{H-NMR}$  at 300 MHz in the presence of optically active shift reagent  $\text{Eu}(\text{hfc})_3$ . In both cases the 90% e.e. was observed from shift of the singlet due to the methyl group attached to the chiral center.

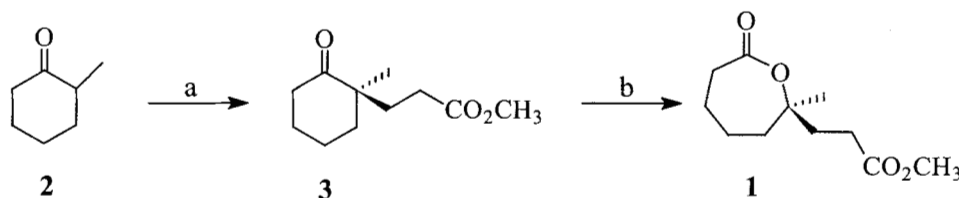
The use of flavor panelists as a means of evaluating sensory properties of a product is somewhat analogous to using an instrument. Therefore, the enantiomers **1** and *ent*-**1** obtained in Scheme 1 were subjected to flavor panelists for sensory evaluation of their odoriferous properties<sup>12</sup>. The samples were evaluated without panelists' previous knowledge of their chemical property or structure. The panel's sensory profile of the two substances is shown in Table 1.

Preliminary evaluations demonstrated that racemic **1** has the lowest aroma intensity and no almond-like notes when comparing with the samples **1** and *ent*-**1**, showing that there is a relationship between the chirality at the six position and the sensory properties of **1**. Racemic **1** was prepared in a similar way than **1** by employing an achiral amine instead S(-)-phenylethylamine as shown in Scheme 2<sup>9,13</sup>.

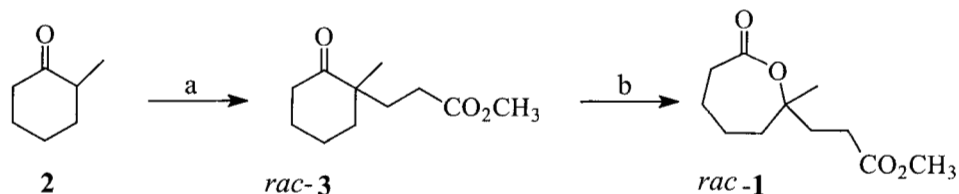
Since the asymmetric Michael addition reaction is an adequate to multigram scale route<sup>8</sup>, the approach shown in Scheme 1 allows to reach a new class of synthetic flavors based on 6,6-disubstituted- $\epsilon$ -caprolactones.

**Table 1.** Sensory properties of **1** and *ent*-**1**.

	pleasant almond-like aroma, sweet notes
	low intensity, described as floral, oily notes



**Scheme 1.** Synthesis of (R)-6-carbomethoxyethyl-6-methyl- $\epsilon$ -caprolactone. a) S(-)-1-phenylethylamine (1.5 eq.), toluene, cat. TsOH, reflux, 1 h, then methyl acrylate (5.0 eq.), r.t., 48 h and 10% aqueous HOAc, r.t., 1 h, 81% yield, 90% e.e.; b) MCPBA (1.0 eq),  $\text{Li}_2\text{CO}_3$  (0.78 eq.),  $\text{CH}_2\text{Cl}_2$ , reflux, 6 h, 65% yield, 90% e.e.



**Scheme 2.** Racemic synthesis of **1**. a) Benzylamine (1.5 eq.), toluene, cat. TsOH, reflux, 1 h, then methyl acrylate (5.0 eq.), r.t., 48 h. and 10% aqueous HOAc, r.t., 1 h, 60% yield; b) See Scheme 1.

## Conclusions

In this work we reported a short and efficient enantioselective synthesis of both enantiomers **1** and *ent*-**1**, based on Baeyer-Villiger reaction preceded by asymmetric Michael addition reaction to introduce the chirality. Since this last reaction is well described in the literature to achieve chiral 2,2-disubstituted cyclopentanones<sup>14</sup> and even other chiral  $\alpha,\alpha$ -disubstituted cyclic ketones, including those having heteroatoms in their rings<sup>8</sup>, the Bayer-Villiger reaction described in this work seems to be attractive to prepare the corresponding chiral lactones as well.

The approach to **1** and *ent*-**1** here described is very promising to achieve synthetic flavors possessing chirality bearing the oxygen in the lactone moiety. The sensory properties of **1** and *ent*-**1**, that add to the existing list in the literature<sup>1-6</sup>, show that modification of the chirality of 6,6-disubstituted- $\epsilon$ -caprolactones can alter the perceived odor. The fact that the enantiomeric forms of **1** show distinct differences in their sensory properties supports the hypothesis that the initial event in the mechanism of the odor perception is enantioselective, leading to diastereoisomeric stimulus-receptor complexes; and these events are transduced to give rise to different odor impressions, the mechanism of which remains to be discovered.

## Experimental Details

### General procedures

The solvents used were of analytical grade and were purified by usual procedures. The chiral auxiliaries S(-)-1-phenylethylamine and R(+)-1-phenylethylamine were purchased from Aldrich Chemical Co. Infrared spectra were recorded with a Perkin-Elmer 1760X spectrophotometer. NMR spectra were recorded with a Brüker AC-300P (300

MHz) spectrometer for solutions in CDCl<sub>3</sub>. Mass spectra (MS) were measured on a Hewlett-Packard 5890-series II instrument equipped with FID detector.

*(R)*-6-carbomethoxyethyl-6-methyl- $\epsilon$ -caprolactone(**1**)

To a suspension of *m*-chloroperbenzoic acid (70% purity, 3.14 g, 14.60 mmol) and lithium carbonate (46 mg, 0.62 mmol) in methylene chloride (26 mL) was added a methylene chloride (6.5 mL) solution of **3** (2.0 g, 10.10 mmol). The mixture was refluxed with stirring for 6 h under an argon atmosphere. The excess peracid was reduced by addition of aqueous sodium sulfite. The mixture was diluted with methylene chloride, washed with aqueous K<sub>2</sub>CO<sub>3</sub> and brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration in vacuum followed by distillation under reduced pressure gave **1** (1.404 g, 65%) as a pale yellow liquid. IR (neat) 2941, 2867, 1735, 1718, 1457, 1438, 1353, 1177, 1106, 1092, 1018 cm<sup>-1</sup>; MS (70eV) 199 (M<sup>+</sup>-15)(2), 137(30), 127(78), 109(50), 99(48), 84(66), 81(100), 55(94), 28(56); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>, COSY)  $\delta$  1.46 (s, 3H, CH<sub>3</sub>), 1.60-1.89 (m, 6H, CH<sub>2</sub>), 1.94 (ddd, 1H, J = 16.7, 13.3 and 8.0 Hz CHCH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 2.16 (ddd, 1H, J = 16.7, 13.3 and 8.0 Hz CHCH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 2.51 (ddd, 2H, J = 16.7, 13.3 and 8.0 Hz, CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 2.69 (ddd, 2H, J = 12.4, 10.7 and 9.7 Hz, CH<sub>2</sub>C=O), 3.71 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>) ppm; <sup>13</sup>C-NMR (CDCl<sub>3</sub>, DEPT)  $\delta$  23.33 (CH<sub>2</sub>), 23.68 (CH<sub>2</sub>), 24.62 (CH<sub>3</sub>), 28.50 (CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 37.00 (CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>), 37.14 (CH<sub>2</sub>COO), 38.97 (CH<sub>2</sub>CH<sub>2</sub>COO), 51.76 (CH<sub>3</sub>O), 82.03 (C), 173.78 (C=O), 174.50 (C=O) ppm.

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