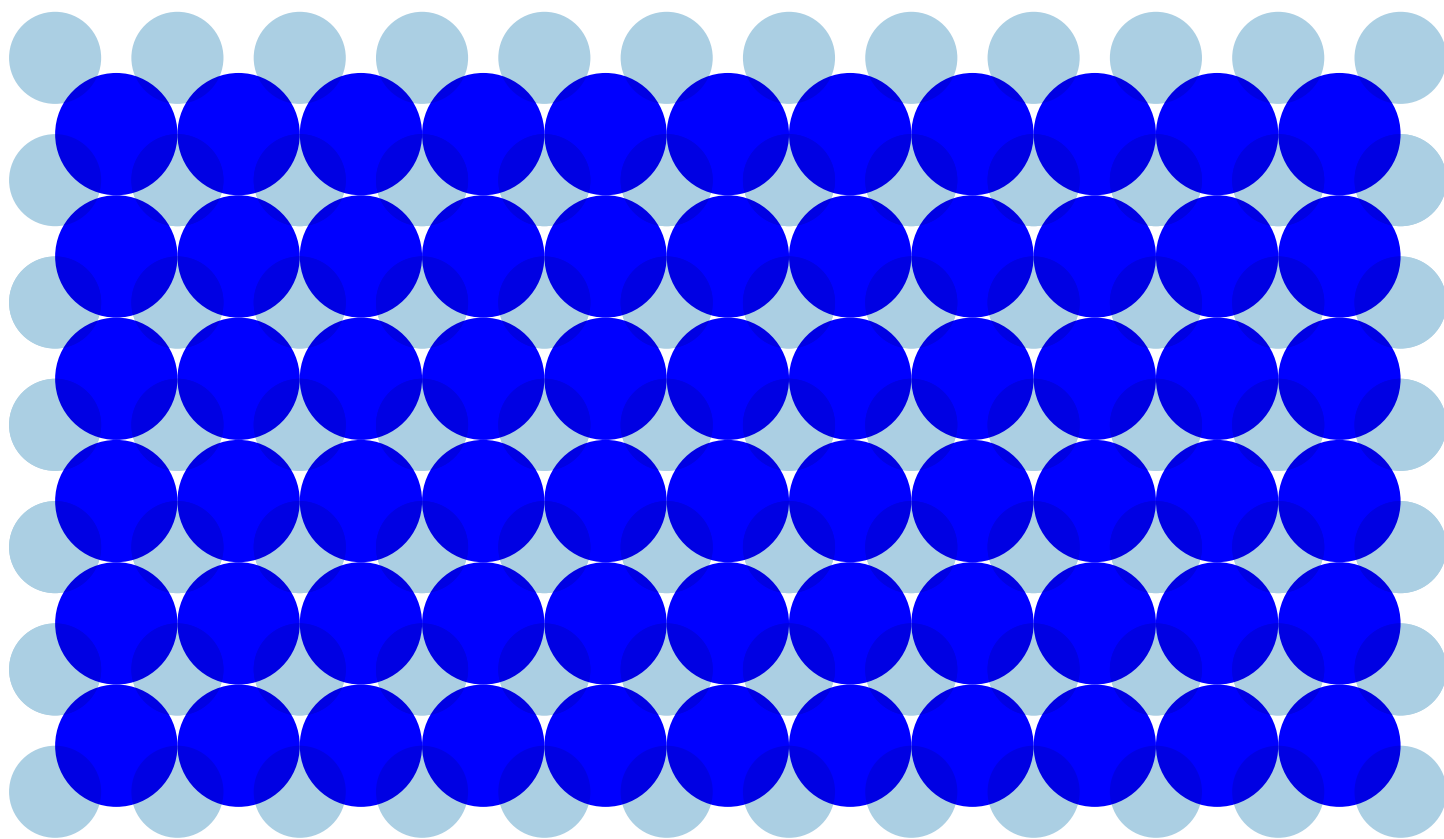


# $\beta$ -Lactones – Extending Aldehydes and Ketones by Two Carbons Through Ketene Addition

Nicola Balice, Dr. Leo Schmid,  
Dr. Leonardo Kleebauer

Have you ever heard of  $\beta$ -lactones? Well, they are important intermediates for the synthesis of various molecules. The finished molecules are used in fragrance, as nutritional supplements, or in liquid crystals. There are multiple pathways to synthesize  $\beta$ -lactones; most of them are based on the addition of one carbon functionality. However, the ketene pathway enables the synthesis of  $\beta$  lactones by adding two carbons, often from naturally present aldehydes and ketones, requiring no pre-preparation. There are more than ten different transformations starting from  $\beta$ -lactones, making use of their reactivity to assemble molecules in a mild and efficient way.

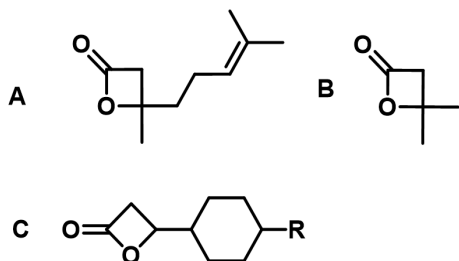


## $\beta$ -Lactones – Extending Aldehydes and Ketones by Two Carbons Through Ketene Addition

$\beta$ -Lactones can be readily synthesized through the addition of ketene to carbonyl groups. They serve as reactive intermediates for various intriguing targets and are applicable in commercial-scale production, thanks to their typically high yields and selectivity. Moreover, these processes are both lean and sustainable.

As of today, the synthesis of  $\beta$ -Lactones via ketene-carbonyl cycloaddition was optimized and patented, because this reaction is one of the few chemical ways inserting two carbons to receive a stable and still reactive intermediate. In Figure 1 are reported examples of patented  $\beta$ -Lactones based on ketene chemistry: **A** is an intermediate in the synthesis of geranic acid derivatives, which are important building blocks in the preparation of perfumes, fragrances, and antiseptic materials.<sup>1</sup> **B** is an intermediate for 3-hydroxy-3-methylbutyric acid and its calcium salt (Ca-HMB), applied in nutritional supplements for muscle growth as they help muscles combat protein breakdown, assist in muscle repair, and support increased endurance. Besides, Ca-HMB are also useful for reducing blood levels of total cholesterol and are used as immuno-stimulants in human and veterinary medicine.<sup>2</sup> **C** is an intermediate in the production of vinyl derivatives with good electric and optical characteristics, which can find useful applications in liquid crystals.<sup>3</sup>

Figure 1. Three differently substituted  $\beta$ -lactones as intermediates in the synthesis of:  $\alpha$ - and  $\beta$ -cyclogeranic acids (A), Ca-HMBs (B) and liquid crystals (C).



The synthesis of the shown examples could be achieved starting from the respective aldehyde or ketone to react with ketene and form the desired  $\beta$ -lactone via [2+2]-cycloaddition (Scheme 1, 1). The reaction is highly efficient, generating minimal waste or byproducts. Additionally, ketones and aldehydes are common functional groups, often naturally present and requiring no pre-preparation.

Nevertheless, there are three alternative pathways also often described (Scheme 1):

- Historically, early developed methods were based on olefins oxidation **2**.<sup>4</sup> Nevertheless, this method comes with significant disadvantages, including poor yields and the reliance on costly palladium and harmful carbon monoxide.
- Another pathway includes carbonylation of epoxides **3**, which can be carried out using tin-<sup>5</sup> or aluminum-<sup>6-7-8-9</sup> porphyrin catalysts. Although this method can be applied on a broad substrate scope and numerous substituents can be inserted on the final  $\beta$ -lactone, the major limitations for an industrial scale application are high pressure carbon monoxide and obviously the nature of epoxides themselves, which are toxic and highly reactive. Furthermore, the synthesis of epoxides must be considered for an overall comparison since they are not always readily available.
- More recently, other strategies using different starting materials have been developed. One of these is carbene chemistry **4** using diazo compounds and Cu catalysts bearing specialized ligands.<sup>10</sup> Despite their wide use in academia as metal-carbene precursors, diazo compounds are often avoided in industry owing to concerns over their instability, exothermic decomposition, and potential explosive behavior.

The three alternatives described only add one carbon to the respective starting material, in contrast to the ketene pathway. The ketene pathway is unique because it allows the addition of two carbons. However, access to ketene is rather the exception than standard. Ketene, a long known and highly reactive material, is unstable and must be reacted further immediately after the formation, for example to produce acetic anhydride, a bulk chemical commonly used for acetylations.

The good news is Arxada operates a dedicated plant in Visp, Switzerland, to produce ketene, a pyrolysis product of acetic acid. Having ketene on-site, the door is open to access a broad spectrum of interesting building blocks, one of them being  $\beta$ -Lactones. Alternatively, Arxada isolate carbon monoxide and oxygen on-site. This is particularly useful when only an alkene is available as a starting material, allowing optimization of the alkene oxidation pathway **2** (Scheme 1).

<sup>1</sup> Patent publication number: WO2000014080.

<sup>2</sup> Patent publication number: WO2012140276.

<sup>3</sup> Patent publication number: EP2020407A1.

<sup>4</sup> Patent publication number: US4533740.

<sup>5</sup> Baral et al. *Catalysts* **2019**, 9, 311.

<sup>6</sup> Getzler et al. *J. Am. Chem. Soc.* **2002**, 124, 7, 1174–1175.

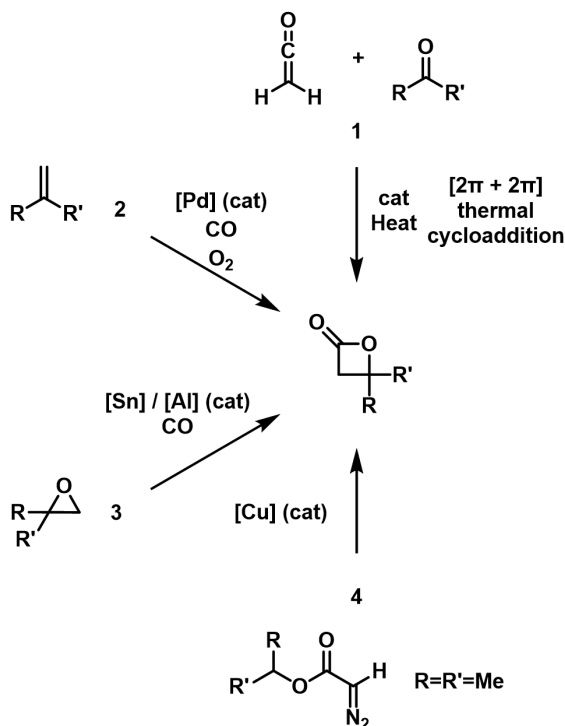
<sup>7</sup> Patent publication number: WO2003050154.

<sup>8</sup> Hubbell et al. *J. Am. Chem. Soc.* **2019**, 141, 6, 2474–2480.

<sup>9</sup> Patent publication number: WO2020102816.

<sup>10</sup> Martín et al. *Org. Biomol. Chem.* **2009**, 7, 4777–4781.

Scheme 1. Possible pathways for the synthesis of  $\beta$ -lactones: 1. Starting from ketones/aldehydes and reacting with ketene; 2. Carbonylation of an olefine in presents of carbon monoxide (CO) and oxygen (O<sub>2</sub>); 3. Carbonylation of an epoxide; 4. Carbene based pathway.



Starting from  $\beta$ -lactones, many transformations to useful functional groups are possible, which may be cumbersome to achieve through other pathways. Scheme 2 gives an overview for some of these transformations:

1. Base-catalyzed ring-opening leads directly to 3-hydroxyesters **1**. In this way,  $\beta$ -hydroxy  $\beta$ -methylbutyrates (HMB, R=Me, R'=H) can be generated, which gain attention in treatment of brain related diseases like Alzheimer or brain damage. The polyester of 3-hydroxybutyric acid, known as PHB, is commonly used as bio-degradable polymer.
2. Esters of 3,3-dimethylacrylic acid (**2**, R=R'=Me) are synthesized by transesterification and dehydration of the corresponding lactone. These esters are used as building blocks for pharma and cosmetic ingredients as well as in flavours and fragrances.

3. Similarly, to PHB, the before mentioned Ca-HMB **3** (R=Me, R'=H) are obtained.
4.  $\beta$ -Lactones can also be opened via nucleophilic attack using ammonia, primary or secondary amines to yield the corresponding amides **4**.
5. Reductive treatment of  $\beta$ -Lactones results in saturated carboxylic acids **5**.
6.  $\beta$ -Lactones can undergo metal-catalyzed ring expansion under high CO pressure to generate variously substituted cyclic anhydrides **6**,<sup>11</sup> which are potent tools for bioconjugation and smart delivery.<sup>12</sup> Hint: Arxada is producing CO on site.
7. If  $\beta$ -lactones are exposed to heat, CO<sub>2</sub> can be liberated and alpha-olefins **7** are formed. Depending on the starting material, linear or branched alpha-olefins are obtained. This strategy may be a lean alternative to Wittig-type C-C bond formation.<sup>13</sup>
8.  $\beta$ -Lactones also undergo ring enlargement to  $\beta$ -lactones **8**.<sup>14-15</sup>
9. Sorbic acid **9** is an example of an industrially implemented process starting from ketene and crotonaldehyde. Sorbic acid and its salts are used as preservatives in the food industry.
10. 3,3-dimethylacrylic acid (**10**, R=R'=Me) is accessed via oligomerisation of  $\beta$ -dimethyl-propiolactone and subsequent depolymerisation. It is used as building block in pharma and cosmetics and is also part of certain pheromones.
11. When treated with Grignard compounds and a catalytic amount of Cu(I) salts,  $\beta$ -lactones can be opened to generate variously substituted saturated carboxylic acids **11**.<sup>16</sup>

These eleven different transformations showcase the broad range for further derivatization. The good news is that Arxada's CDMO team is skilled and equipped to develop these reactions for individual molecules, from feasibility studies to production, scaling up from a kilogram scale to a final multi-ton scale.

<sup>11</sup> Getzler et al. *J. Am. Chem. Soc.* **2004**, *126*, 6842-6843.

<sup>12</sup> Spanedda et al. *Bioconjugate Chem.* **2021**, *32*, 3, 482-496.

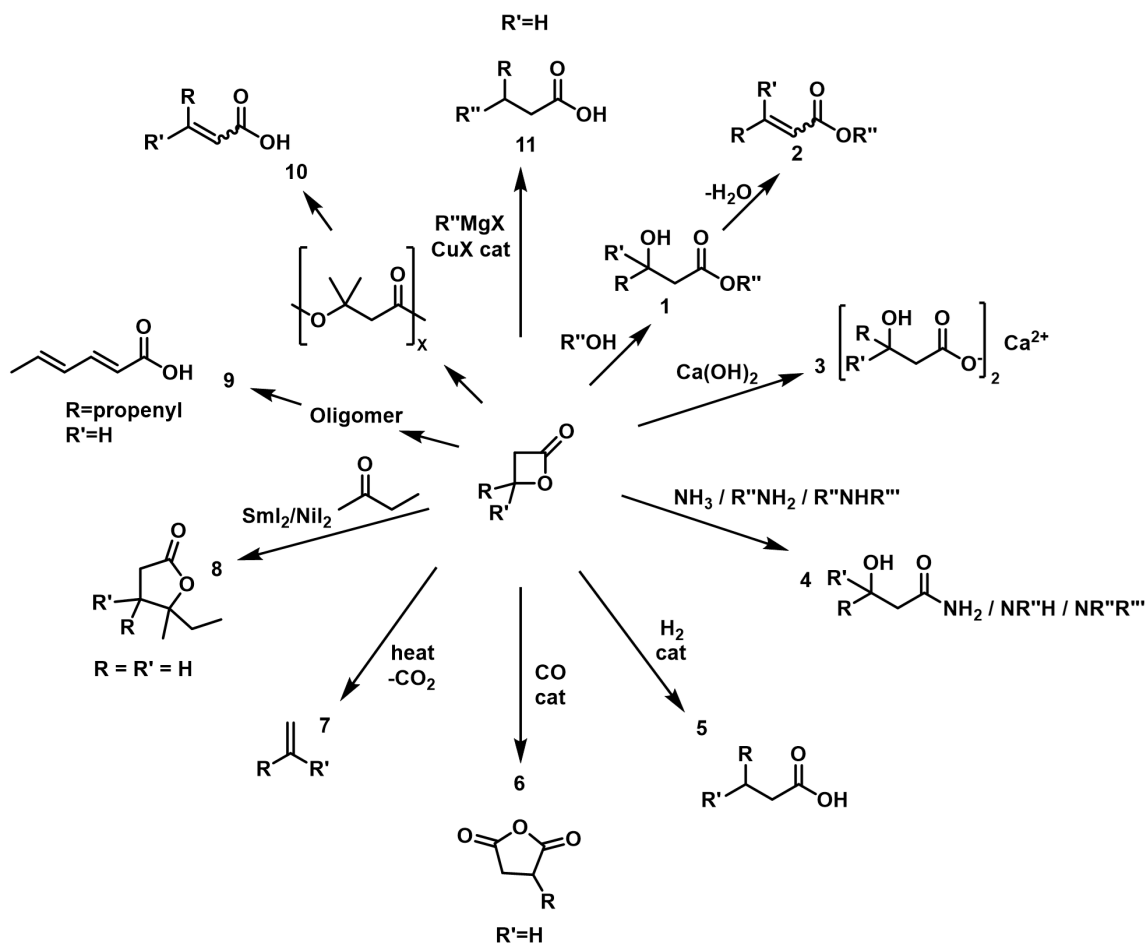
<sup>13</sup> Moldoveanu, *Pyrolysis of Organic Molecules (Second Edition), Applications to Health and Environmental Issues*, **2019**, 635-696.

<sup>14</sup> Crich et al. *e-EROS Encyclopedia of Reagents for Organic Synthesis*, **2008**, 1-2.

<sup>15</sup> Mulzer et al. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 13-14.

<sup>16</sup> Lipshutz et al. *Organic Reactions*, **1992**, 41.

Scheme 2.  $\beta$ -Lactones as versatile building blocks for derivatization.

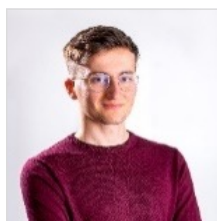


In summary,  $\beta$ -lactones can be easily synthesized via ketene-carbonyl reaction using in situ generated ketene at the Arxada Visp site. This method is fast and efficient and does not require expensive metal catalysts, high pressure toxic gas or commercially unavailable and hazardous starting materials. Finally, the thus generated  $\beta$ -lactones also serve as excellent building blocks for subsequent modifications.

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## Author(s) information



**Nicola Balice**  
Trainee R&D Chemist

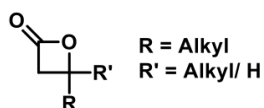


**Leo Schmid**  
Senior R&D Chemical Engineer  
Technical Chemical Evaluation  
& Development



**Leonardo Kleebauer**  
Global Key Account Manager CDMO  
[leonardo.kleebauer@arxada.com](mailto:leonardo.kleebauer@arxada.com)

## Our offer



- **One-step synthesis of  $\beta$ -lactones from kg to mt**
- **Ketene reagents' backward integration**
- **Carbon monoxide backward integration**
- **Ability to derivatize on-demand**
- **Focus on *what matters to you***

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Arxada Ltd.  
Muenchensteinerstrasse 38  
4002 Basel, Switzerland  
Tel: +41 61 316 81 11  
[email@arxada.com](mailto:email@arxada.com)

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