

Synthetic Strategies toward Lactones Identified through *Science of Synthesis*: A Comparative Case Study



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Abstract

Given our ongoing interest in intermolecular cyclization reactions, the synthesis of lactones (Figure 1) was selected for a representative case study. *Science of Synthesis* was employed as a structure-based planning tool to identify and evaluate complementary lactonization strategies, enabling rapid method selection and informed retrosynthetic design.

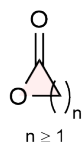


Figure 1 General Structure of Lactones

Discussion

Lactones are cyclic esters that occur widely in natural products, pharmaceuticals, and functional materials. Their ring sizes range from three-membered to macrocyclic systems, although five- and six-membered lactones are generally the most thermodynamically favored. Beyond their structural relevance, lactones play key roles in medicinal chemistry by modulating lipophilicity, conformational rigidity, and binding selectivity. A representative example is lovastatin (Figure 2), in which the lactone unit is essential for biological activity.

Because of their broad applicability, the development of efficient and selective methods for preparing lactones beyond the classical Baeyer–Villiger oxidation remains a central objective in synthetic organic chemistry. In this case study, guided by *Science of Synthesis*, we examine a range of strategies for lactone construction.

Science of Synthesis was employed as a synthetic planning tool by utilizing its structure-based search functionality. A lactone substructure was used as the key query element, enabling the rapid identification of validated and complementary approaches for the intramolecular formation of esters. This search strategy facilitated direct access to authoritative procedures, and information about key reaction conditions, substrate scope, and limitations; the suggested methods were subsequently evaluated from a retrosynthetic perspective. Six general disconnections leading to the lactone core were identified (Scheme 1).

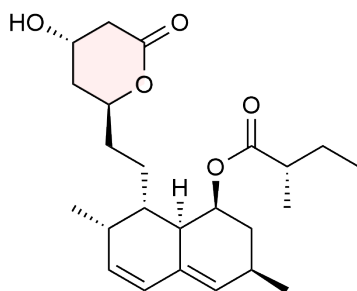
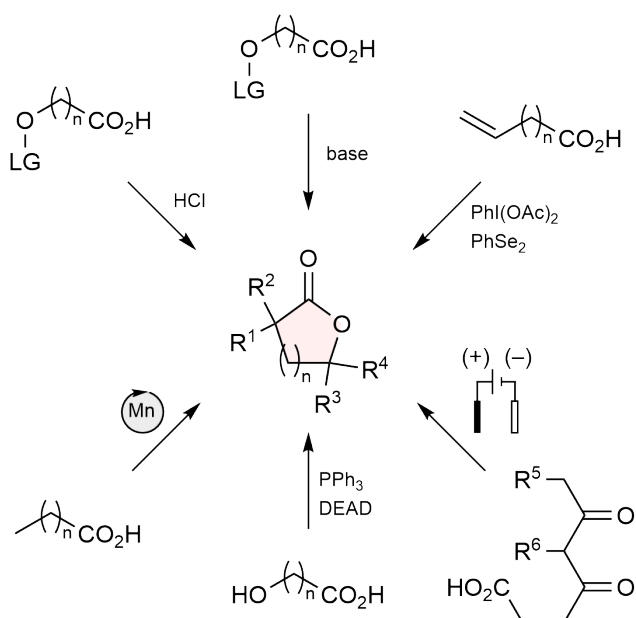


Figure 2 Structure of Lovastatin



Scheme 1 Synthetic Routes for the Synthesis of Lactones; LG = leaving group

Within a *Science of Synthesis* chapter devoted to the synthesis of lactones (Section 20.6),^[1] two excellent subsections on lactonization reactions were identified as being particularly helpful. Cyclization under mild acidic conditions (Section 20.6.1.1.1) provides a straightforward and operationally simple approach to lactones. However, this method is limited when acid-labile protecting groups are present and is most effective for the formation of five- and six-membered rings. On the other hand, base-promoted cyclization (Section 20.6.1.3.1) offers a complementary strategy that is particularly valuable for acid-sensitive substrates. This approach shows broader functional-group compatibility and can be applied to the synthesis of macrolactones, although conformational preorganization of the precursor is often required.

In the case of unsaturated alkenoic acids as substrates, as described in Section 20.6.1.7, the use of electrophilic selenium reagents enables rapid intramolecular cyclization. Our searches in *Science of Synthesis* quickly directed us to a useful method to access lactone cores based on the in situ generation of an electrophilic selenium species from $\text{PhI}(\text{OAc})_2$ and $(\text{PhSe})_2$. This strategy is particularly useful for the synthesis of medium- and large-ring systems.

A recently developed methodology based on manganese-catalyzed oxidative lactonization (*Base-Metal Catalysis*, Section 2.12.3.1)^[2] offers an enantioselective and sustainable alternative. The use of an earth-abundant metal, combined with high stereo control, makes this methodology especially attractive for the synthesis of enantioenriched lactones.

The Mitsunobu reaction (Section 20.6.1.6) provides a reliable method for intramolecular esterification using diethyl azodicarboxylate (DEAD) and triphenylphosphine, particularly when inversion of configuration is required at the alcohol-bearing stereocenter.

Lastly, an electrochemical strategy enables the enantioselective conversion of dioic acids into spiro-fused lactones using chiral iodoarenes as mediators (*Electrochemistry in Organic Synthesis*, Section 12.1.1.2).^[3] This approach avoids the use of stoichiometric chemical oxidants and represents a sustainable alternative for the construction of complex lactone architectures.

As a final point to note, a *Science of Synthesis* Knowledge Updates contribution on the topic of lactone synthesis has recently been published, providing a comprehensive and up-to-date overview of key recent advances.^[4] This further strengthens the information available on the platform for identifying the most useful routes to these important compounds.

Conclusion

This case study demonstrates that *Science of Synthesis* is a powerful platform for retrosynthetic planning. Its structure-based search capabilities enable the rapid identification and evaluation of complementary lactonization strategies, allowing the selection of optimal conditions based on substrate structure, functional-group compatibility, ring size, and stereochemical requirements. Moreover, the searches guide the user to key articles devoted to the synthesis of specific classes of compounds (such as lactones), quickly providing an overview of the most significant approaches. At the same time, related transformations may be covered in other reviews in the context of particular enabling technologies, such as electrochemistry. As such, the platform plays a central role in translating synthetic concepts into practical and reliable laboratory solutions.

References

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