OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

# Synthesis of γ-Lactones Utilizing Ketoacids and Trimethylsulfoxonium Iodide

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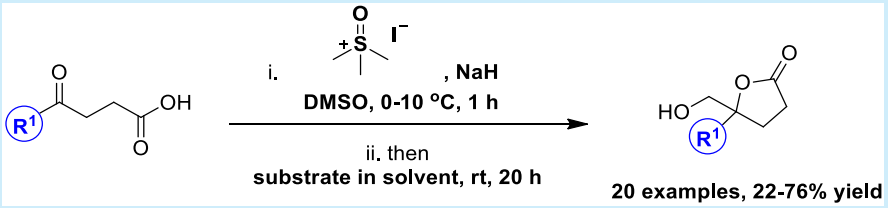
Supporting Information




**ABSTRACT:** The Johnson−Corey−Chaykovsky epoxidation is one of the oldest methods for the synthesis of terminal epoxides from carbonyl compounds. Herein we present a simplified extension of the Johnson−Corey−Chaykovsky epoxidation, where ketoacids are employed as the substrates and commercially available trimethylsulfoxonium iodide is employed as the carbon-atom homologating reagent. A variety of lactones are produced in a single step in synthetically useful yields.



During the last 60 years, organo-sulfur compounds have attracted the attention of the scientific community as valuable intermediates in the synthesis of various organic compounds and as key components of numerous reactions.[1] In particular, sulfur ylides have been recognized for their important role as a source of carbanions.[2] The Johnson−Corey−Chaykovsky epoxidation is among the oldest methods for the synthesis of structurally diverse terminal oxiranes from aldehydes or ketones.[3] Several modifications of the reaction have been investigated via the alteration of the base, the medium of the reaction, or the insertion group.[4] Very recently, attention has been diverted to asymmetric variations of the reaction, employing chiral sulfides,[5] and its applications in asymmetric catalysis with chiral catalysts.[6] In this work, we extend the limits of the Corey−Chaykovsky epoxidation to the synthesis of lactones.

Lactones are important intermediates in organic synthesis and have been widely employed for the preparation of antimicrobial compounds,[7] compounds of biological importance,[8] and a variety of useful building blocks[9] (Figure 1).

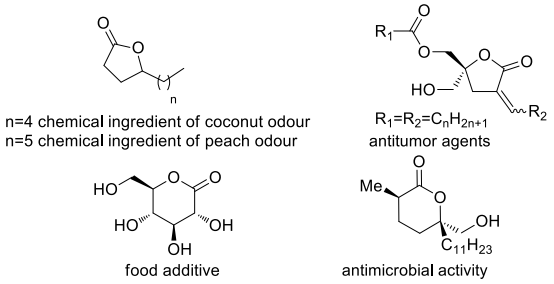
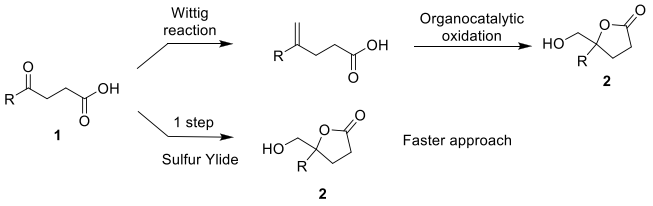



**Figure 1.** Utility of the lactone's skeleton.

Because of the importance of the lactone moiety, a variety of synthetic pathways have been reported for their synthesis, utilizing as starting materials a plethora of compounds, like unsaturated hydrocarbons,[10] alcohols,[11] or carboxylic acids.[12] A very common approach is the intramolecular lactonization of organic compounds to γ-lactones, utilizing a variety of metal catalysts[13] or organocatalysts.[14]

Our group has focused on the implementation of green strategies for the synthesis of compounds via new reactions employing either organocatalysis[15] or photocatalysis.[16] Herein we contribute to the synthesis of lactones via an alternative and complementary methodology (Scheme 1). Because of our knowledge of oxidation and especially epoxidation,[15] we have reported the synthesis of lactones **2** from **1** via a two-step process involving a Wittig olefination, followed by an organocatalytic epoxidation−cyclization (Scheme 1, top).[15c] We have also provided photocatalytic alternatives, starting from either alkenes and iodoacetic acid[16d] or Michael

**Scheme 1. Synthetic Pathways for the Synthesis of Lactones 2**




**Received:** May 28, 2019




DOI: 10.1021/acs.orglett.9b01852
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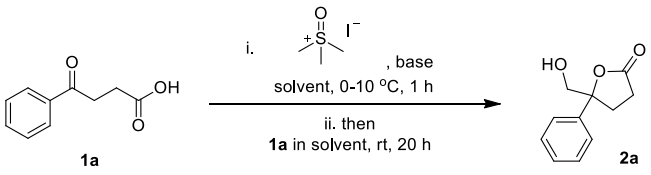
acceptors and alcohols.[16b] However, it would be highly desirable if we could provide a one-step procedure for the direct transformation of **1** to lactones **2**. Herein we saw an opportunity that sulfur ylides provide[17] to perform such a task.

We initiated our study utilizing ketoacid **1a** in an attempt to identify the optimum reaction conditions for the synthesis of γ-lactone **2a** (Table 1). In the beginning, sodium hydride was

**Table 1. Optimization of the Reaction Conditions for the Synthesis of γ-Lactones from Ketoacids**[a]



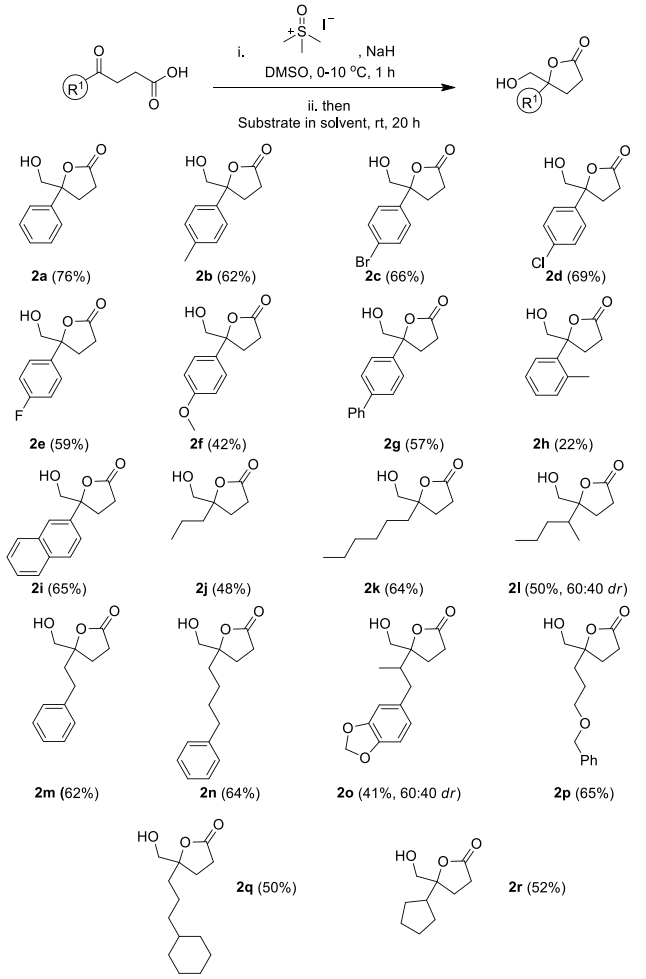

| entry | base (equiv) | solvent (M) | yield (%)[b] |
|---|---|---|---|
| 1 | NaH (1.2) | THF (0.2) | 0 |
| 2 | NaH (1.2) | $CH_2Cl_2$ (0.2) | 9 |
| 3 | NaH (1.2) | MeCN (0.2) | traces |
| 4 | NaH (1.2) | DMSO (0.2) | 55 |
| 5 | K$^t$OBu (1.2) | DMSO (0.2) | 27 |
| 6 | *n*-BuLi (1.2) | DMSO (0.2) | 51 |
| 7 | KHMDS (1.2) | DMSO (0.2) | 5 |
| 8 | DBU (1.2) | DMSO (0.2) | 0 |
| 9 | NaH (2.4) | DMSO (0.2) | 68 |
| 10 | NaH (3.6) | DMSO (0.2) | 76 |
| 11 | NaH (3.6) | DMSO (0.4) | 41 |
| 12 | NaH (3.6) | DMSO (0.1) | 70 |

[a]Reaction conditions for lactonization: ketoacid (1.0 equiv), trimethylsulfoxonium iodide (3.0 equiv), base, solvent at 0 °C for 1 h, and then rt for 20 h. [b]Isolated yield.

employed as the base to form in situ the sulfur ylide, and several solvents were tested, but the desired lactone was not obtained in satisfactory yield (Table 1, entries 1−3). When DMSO was used as the solvent, lactone **2a** was afforded in good yield (Table 1, entry 4). Various organic bases were then tested along with trimethylsulfoxonium iodide, with sodium hydride leading to the highest yield (Table 1, entries 5−8). Because trimethylsulfoxonium iodide is employed, a common cheap base can be employed for the deprotonation rather than a stronger organic base, which is required for sulfonium ylides (p$K_a$ $Me_3S(O)I$ = 18.2, p$K_a$ $Me_3S$ = 24.5 (in DMSO)).[18] Furthermore, an increase in the equivalents of the base afforded lactone **2a** in better yield (Table 1, entries 9 and 10). When the concentration of DMSO was altered, the yield decreased (Table 1, entries 11 and 12).

Having in hand the optimized reaction conditions, we further explored how the nature of the substrate affects the reaction outcome (Scheme 2). Various substituents at the para position of the aromatic ring had no significant impact on the reaction outcome, leading to similar yields (Scheme 2, **2b−g**). In the case of ortho-substituted ketoacid **1h**, the yield dropped, affording lactone **2h** in low yield. The high stereochemical congestion close to the carbonyl moiety, where the reaction takes place, probably slows down the desired reaction. The naphthyl group does not affect the reaction outcome, and lactone **2i** was isolated in 65% yield. Changing the substitution pattern by using aliphatic moieties did not alter the behavior of the reaction (Scheme 2, **2j−l**). Furthermore, the use of aliphatic side chains with phenyl or other functional groups

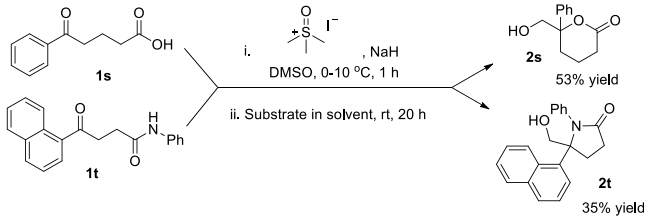
**Scheme 2. Substrate Scope for the Synthesis of γ-Lactones from Ketoacids**




expanded the substrate scope, leading to high yields (compounds **2m−r**).

In an effort to further expand the possibilities of this protocol, additional substrates were tested, affording a variety of cyclic products (Scheme 3). Starting from ketoacid **1s** under

**Scheme 3. Additional Substrate Scope**




the same reaction conditions, δ-lactone **2s** was afforded in good yield. Thus the method can be extended in the synthesis of δ-lactones. Finally, another possibility for the synthesis of lactams is possible because ketoamide **1t** was used as a substrate and γ-lactam **2t** was isolated in moderate yield. Attempts to prepare substituted sulfoxonium or sulfonium salts and utilize them in our methodology to widen our substrate scope were met with failure.

To expand the limits of this method, we envisaged the application of our protocol in a fast total synthesis of the



DOI: 10.1021/acs.orglett.9b01852
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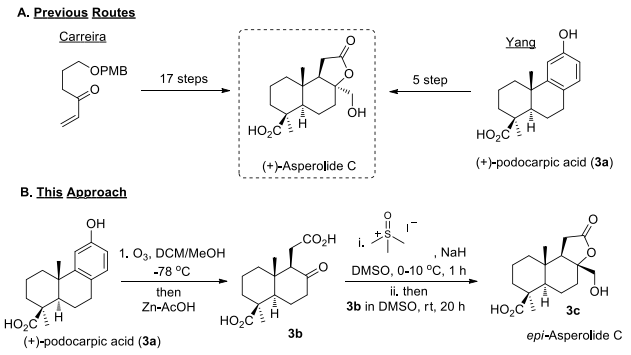
natural product (+)-asperolide C[19] in only two steps, starting from (+)-podocarpic acid (**3a**) (Scheme 4). Podolactones and

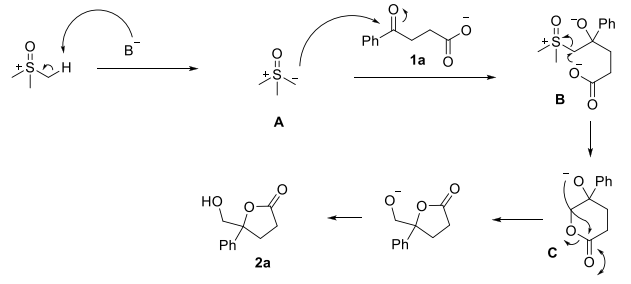
**Scheme 4. Synthetic Routes to (+)-Asperolide C**




other related compounds of natural origin show a wide variety of biological activities.[20] Because of this biological activity, different research groups, in the last years, have accomplished the total synthesis of the natural product (+)-asperolide C through many synthetic steps.[21] Carreira and coworkers were the first to report the total synthesis of (+)-asperolide C in 17 steps (Scheme 4).[21a] In 2016, Yang and coworkers reported the synthesis of (+)-asperolide C in five steps.[21b] Utilizing our methodology, we envisaged a fast two-step assembly of (+)-asperolide C from commercially available (+)-podocarpic acid (**3a**) (Scheme 4). In the first step, ozonolysis of (+)-podocarpic acid (**3a**), followed by the reduction of the resulting hydroperoxide, afforded keto diacid **3b**; all data matched with literature.[21b] In the final step, the application of our methodology utilizing trimethylsulfoxonium iodide and sodium hydride led to product **3c** in 24% yield over two steps. Unfortunately, **3c** was not (+)-asperolide C but its epimer. Because all chiral centers in **3b** are fixed and previous methodologies employed a substrate-controlled epoxidation of the ester-protected compound, we believe that the free carboxylate, in conjunction with the sulfur−ylide reactivity, instead of a peracid, leads to a neighboring-effect-controlled (electrostatic interaction between the carboxylate and the ylide[22]) transition state, which is responsible for this difference.

To summarize the events that take place in this reaction, a proposed reaction mechanism is shown in Scheme 5.

**Scheme 5. Proposed Reaction Mechanism**




Trimethylsulfoxonium iodide is deprotonated by sodium hydride, and the corresponding sulfur ylide **A** is formed.[17,23] In the next step, the intermediate ylide attacks the keto group of the deprotonated ketoacid **1a**, affording intermediate **B**; then, the deprotonated acid group attacks the carbon that bears the sulfoxonium group, leading to six-membered lactone **C**.[24] The alkoxide **C** undergoes an intramolecular ring opening of the six-membered ring lactone to the desired γ-lactone **2a**. The alternative mechanism involving epoxide formation, followed by an $S_N2$-type reaction at a quaternary carbon atom, seems unlikely to be happening.

In conclusion, an effective and easy-to-handle synthetic protocol for the synthesis of γ-lactones from ketoacids is described. Utilizing a modification of the Johnson−Corey−Chaykovsky reaction, a variety of γ-lactones were synthesized. A plethora of substituted ketoacids lead to γ- or δ-lactones as well as lactams in good to excellent yield. An effort to apply our methodology to the total synthesis of (+)-asperolide C was demonstrated. Unfortunately, its epimer was obtained, which opens new avenues to synthesize these compounds that have never been described or assessed for their biological activity.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01852.

Experimental procedures, full optimization data, characterization data, and NMR spectra (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support through the Special Account for Research (ELKE) and the Laboratory of Organic Chemistry of the National and Kapodistrian University of Athens. We thank Ms. Iokasti Dodi (Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens) for preliminary results and Dr. Dimitra Benaki (Department of Pharmacy, National and Kapodistrian University of Athens) for her assistance in acquiring the NMR spectra of 3c. I.T. thanks the Hellenic Foundation for Research and Innovation (HFRI) and the General Secretariat for Research and Technology (GSRT) for an HFRI Ph.D. Fellowship grant (GA14476). Also, COST Action C−H Activation in Organic Synthesis (CHAOS) CA15106 is acknowledged for helpful discussions.

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(24) We thank one of the referees for his fruitful suggestions regarding the reaction mechanism.



DOI: 10.1021/acs.orglett.9b01852
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