

Diastereoselective Synthesis of γ -Lactones through Reaction of Enediolates with α,β -Unsaturated Sulfoxonium Salts

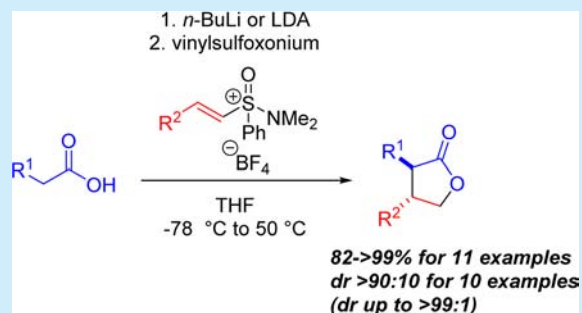
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S Supporting Information

ABSTRACT: Studies of the reaction of lithium enediolates with α,β -unsaturated sulfoxonium salts are described. γ -Lactones were formed in very good to excellent yields (82% \rightarrow 99% for 11 examples) and with very good to excellent diastereoselectivity (dr >90:10 for 10 examples), favoring the *trans*-diastereomer.



γ -Lactones are molecules that have attracted great interest from synthetic organic chemists due to their diverse range of biological activities and the challenges that their stereoselective synthesis presents (Figure 1).¹

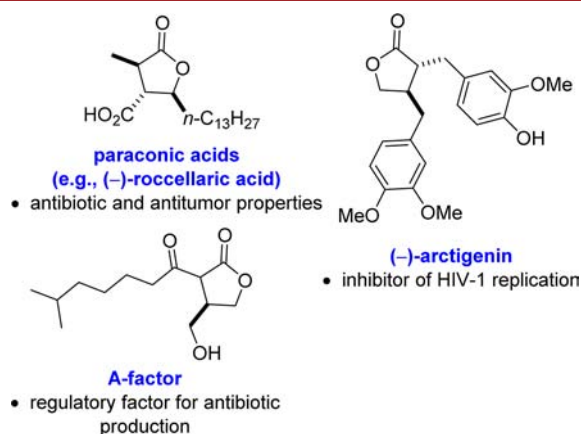
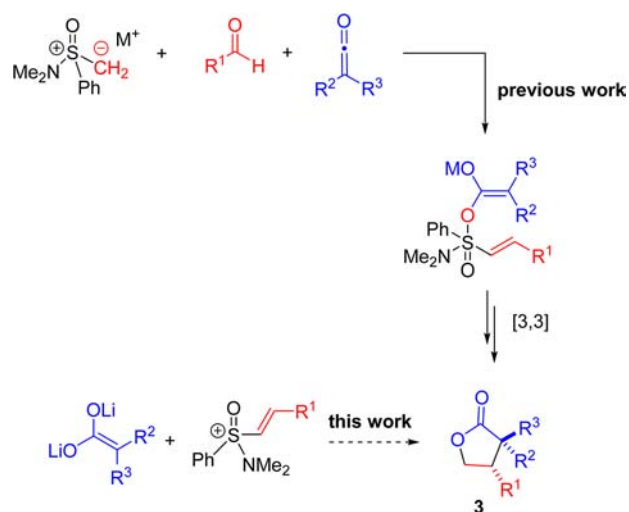


Figure 1. Biologically active monocyclic γ -lactones.

Recently, we developed a diastereoselective method for γ -lactone synthesis from the reaction of an aminosulfoxonium ylide with aldehydes and ketenes (Scheme 1).^{2,3} We originally proposed that a [3,3]-sigmatropic rearrangement of a sulfuran oxide intermediate was responsible for the good diastereoselectivity observed in that reaction.^{2,4} To explore the mechanism further, we reasoned that the putative sulfuran oxide intermediate might be accessed through an independent route involving reaction of a lithium enediolate with a vinylsulfoxonium salt.^{5,6} Several decades ago, Johnson and co-workers investigated the reactions of vinylsulfoxonium salts

Scheme 1. Proposed New Method for Diastereoselective γ -Lactone Synthesis



with a variety of nucleophiles.⁶ However, surprisingly, no work had been carried out investigating lithium enediolates as nucleophiles in reactions with vinylsulfoxonium salts.⁶ More recently, Aggarwal's group and others have investigated the reactions of various nucleophiles (amines, amino alcohols, etc.) with vinylsulfoxonium salts to give a diverse range of monocyclic and bicyclic products.^{7,8} As our work neared completion, Zakarian and co-workers showed that lithium enediolates, in the presence of chiral amine ligands, could undergo conjugate addition to acrylates, with high diastereoselectivity and

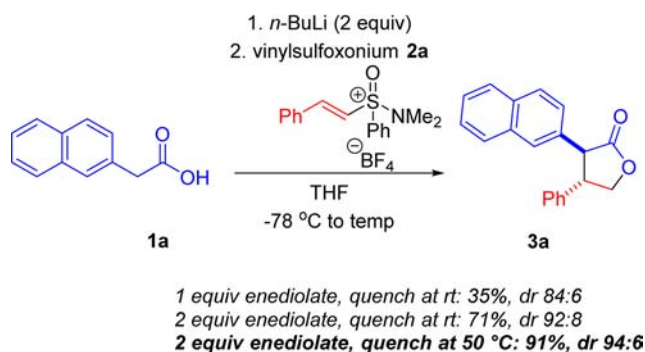
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enantioselectivity.⁹ In this paper, we report that the reaction of lithium enediolates with vinylsulfoxonium salts provides an efficient and highly diastereoselective route to γ -lactones.

We began reaction optimization by investigating the reaction of 2-naphthyl-2-acetic acid with phenyl-substituted sulfoxonium salt **2a** at -78 °C. The sulfoxonium salt was prepared by procedures previously described by Johnson and co-workers.⁶ It was found that the reaction gave the best yields of the desired γ -lactone when 2 equiv of the enediolate reactant, generated through treatment of the carboxylic acid with *n*-BuLi, was added to **2a** in THF at -78 °C. Another important consideration was the temperature at which the reaction was quenched. When the reaction was quenched with dilute HCl at 50 °C, **3a** was afforded in the best yield and with optimal diastereoselectivity (Scheme 2). Quenching the reaction at a

Scheme 2. Optimization of Diastereoselective γ -Lactone Synthesis



relatively elevated temperature allowed for the reaction to reach completion and also for equilibration to the *trans*-diastereomer to occur. Interestingly, quenching the reaction at low temperature (-78 °C) did not change the identity of the major diastereomer but did lead to much lower diastereoselectivity.

X-ray crystallographic analysis of recrystallized **3a** revealed that the major diastereomer produced by the reaction was the *trans*-diastereomer. During this time other vinyl onium salts were evaluated for comparison, e.g., vinyltriphenylphosphonium bromide, vinyldimethylsulfonium triflate, and vinyl-diphenylsulfonium triflate.⁷ However, none of the other salts gave as good results as were observed with the vinylsulfoxonium salts **2**. The scope of the reaction with respect to variation of both carboxylic acid and vinyl sulfoxonium salt structure was then explored.

The reaction proved to be tolerant of a variety of aryl substituents α to the carboxyl group, including both electron-donating and electron-withdrawing substituents. Interestingly, even substitution at the 2-position on aryl substituents was tolerated without any significant effect on yield in reactions with styrenyl sulfoxonium salt **2a** (Table 1, entries 1–7). However, a significant decrease in reaction efficiency was detected when 2-alkyl-substituted carboxylic acids were used ($R^1 = t$ -Bu, entry 8). Furthermore, placing a less branched alkyl substituent at the 2-position led to lower diastereoselectivity with similar yield to the *t*-Bu-substituted example (e.g., for $R^1 = i$ -Bu, dr 74:26). Good results were also achieved with the *i*-Pr-substituted vinyl sulfoxonium salt **2b** (entries 9–12). Invariably, high diastereoselectivity, favoring formation of the *trans*-diastereomer as the major isomer, was achieved.

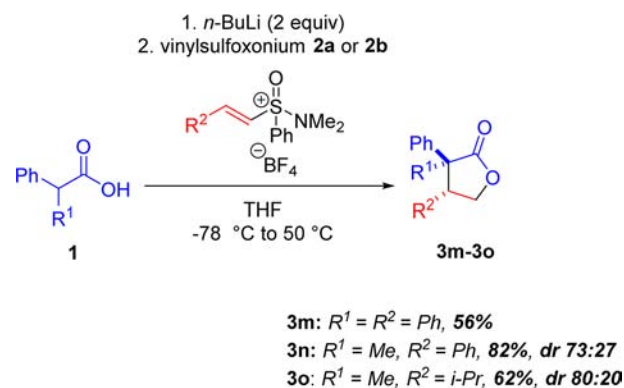
Table 1. Substrate Scope of γ -Lactone Synthesis

entry	R ¹	R ²	yield ^a (%)	dr ^b	3
1	2-Naph	Ph	91	94:6	3a
2	Ph	Ph	89	97:3	3b
3	2-MeOPh	Ph	99	92:8	3c
4	3-MeOPh	Ph	92	96:4	3d
5	2-MePh	Ph	89	88:12	3e
6	3-MePh	Ph	82	97:3	3f
7	2-ClPh	Ph	92	89:11	3g
8 ^c	<i>t</i> -Bu	Ph	33	>99:1	3h
9	2-Naph	<i>i</i> -Pr	98	92:8	3i
10	Ph	<i>i</i> -Pr	>99	92:8	3j
11	2-ClPh	<i>i</i> -Pr	54	94:6	3k
12	3-MePh	<i>i</i> -Pr	83	92:8	3l

^aIsolated yield (%) for both diastereomers. ^bdr = diastereomeric ratio represents ratio of major diastereomer to minor diastereomer; determined by GC-MS or ¹H NMR analysis of crudes. ^cLDA (2 equiv) used as base.

The reactions of lithium enediolates derived from α,α -disubstituted acetic acids were also investigated (Scheme 3).

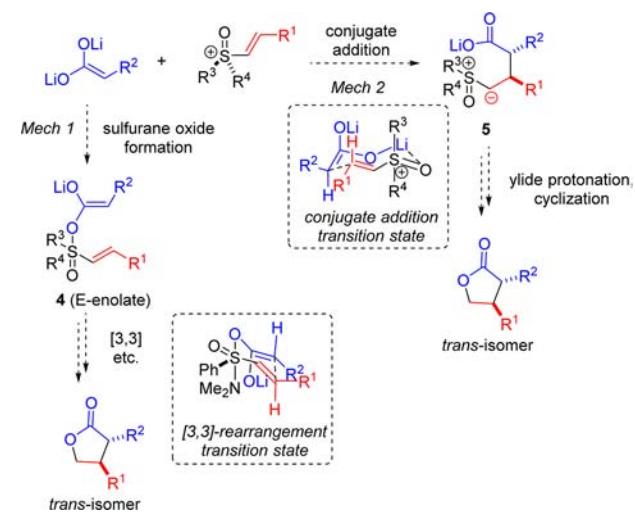
Scheme 3. Formation of γ -Lactones Bearing a Quaternary Center



The reactions were found to proceed smoothly to provide access to the desired α -quaternary center substituted γ -lactones, albeit with lower diastereoselectivity (e.g., for **3o**, dr 80:20).² The lower diastereoselectivity may be attributed to the inability of **3n,o** to undergo equilibration (through reversible deprotonation–protonation) or because of the closer similarity of the methyl and phenyl substituents' size (compared to hydrogen and phenyl substituents) and the lack of steric bias therein.

We suggest that there are two possible mechanisms by which γ -lactone **3** could be formed. In the first pathway, Mech 1 (Scheme 4), the lithium enediolate adds to the sulfur of vinylsulfoxonium salt **2** to give *E*-enolate intermediate **4** in stereoselective fashion. Subsequent [3,3]-sigmatropic rearrangement, ylide protonation (by lactone/acid/intramolecular proton transfer), and cyclization would lead to the formation of

Scheme 4. Possible Reaction Mechanisms



lactone **3** as the *trans*-diastereomer.^{2,4} This mechanism is consistent with the one we have proposed for the formation of γ -lactones from sulfoxonium ylide, ketenes, and aldehydes in that both involve enolate **4** as a key intermediate.^{2,3} Indeed, it was noted that the same major diastereomer was formed from the reaction of 2-phenylpropionic acid with vinylsulfoxonium **2b** (yield = 62%, dr = 80:20), as was obtained from the three-component reaction of aminosulfoxonium ylide with isobutyraldehyde and methylphenylketene (yield = 33%, dr = 92:8).²

Alternatively, ylide intermediate **5** could be formed through conjugate addition of lithium enediolate to the β -position of vinylsulfoxonium **2** (Mech 2, Scheme 4).⁹ Protonation of ylide **5** (by lactone/acid/intramolecular proton transfer) followed by cyclization would provide access to γ -lactone **3**. Such a mechanism could also account for the high *trans*-diastereoselectivity observed if a closed transition state (through Li chelation) was involved in the conjugate addition step (Scheme 4).¹⁰

In conclusion, we report that the reaction of lithium enediolates with vinylsulfoxonium salts provides an efficient and highly diastereoselective route to γ -lactones. This versatile method complements our recently reported one-pot methodology for the preparation of γ -lactones from disubstituted ketenes in that it mainly provides access to γ -lactones bearing α - and β -tertiary stereogenic centers. Future studies will focus on the development of an asymmetric variant of the reported reaction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectroscopic data for all new compounds, X-ray data for lactone **3a** (CIF), and NOESY for **3n**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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