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# Butyrolactone Synthesis via Polar Radical Crossover Cycloaddition Reactions: Diastereoselective Syntheses of Methylenolactocin and Protolichesterinic Acid

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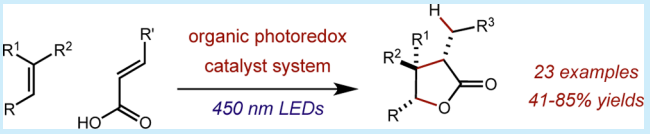
Supporting Information

**ABSTRACT:** A direct catalytic synthesis of γ-butyrolactones from simple alkene and unsaturated acid starting materials is reported. The catalytic system consists of the Fukuzumi acridinium photooxidant and substoichiometric quantities of a redox-active cocatalyst. Oxidizable alkenes such as styrenes and trisubstituted aliphatic alkenes are cyclized with unsaturated acids via polar radical crossover cycloaddition (PRCC) reactions. This method has been applied to the diastereoselective total synthesis of methylenolactocin and protolichesterinic acid.




γ-Butyrolactones are prevalent heterocycles in naturally occurring isolates that often possess a broad range of bioactivity including antibacterial, antifungal, antiviral, and anti-inflammatory properties.[1] Increased bioactivity is commonly observed for γ-butyrolactones possessing an α-methylene moiety, which is often implicated as the active pharmacophore.[2] The paraconic acids are a family of γ-butyrolactones with extensively documented medicinal properties and have been the target of synthetic studies for a number of years (Figure 1).[3] Methylenolactocin, isolated by Park and co-workers, was found to possess unique antibacterial activity[4] and has been previously synthesized by Greene,[5] and others,[3,6] in diastereoselective and enantioselective multistep syntheses. Similarly, protolichesterinic acid exhibits antifungal activity and inhibitory activity toward colon carcinoma,[7,8] and enantioselective syntheses have been reported.[9]

Because of their pronounced medicinal function, γ-butyrolactones are appealing targets for study and have spawned numerous general methods for their synthesis.[10] Highlights for the synthesis of γ-butyrolactones include variations of the catalytic enal−aldehyde annulation[11] and halolactonization. Several examples for the direct synthesis of α-methylene γ-butyrolactones are known, including the Drieding−Schmidt reaction,[12] allylboration,[13] enyne cyclizations,[14] and Pd(II)-catalyzed acylation−lactonization reaction.[15] Unfortunately, these reports often require highly prefunctionalized starting materials, which can often restrict the structural diversity of the lactones constructed employing these methods.

We envisioned that a direct method to form γ-butyrolactones with α-methylene or α-alkylidine functionalities might be achieved via organic photoredox catalysis.[16] We also hypothesized that such a method could be used to access members of the paraconic acid family by further elaboration of the γ-butyrolactone products. We have previously reported the addition of nucleophiles to oxidizable alkenes using the Fukuzumi acridinium photooxidant[17,18] in conjunction with a redox-active hydrogen atom donor in the development of anti-

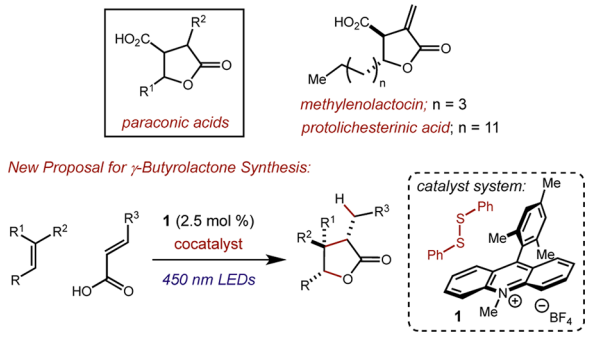



**Figure 1.** Biologically active γ-butyrolactones.

Markovnikov alkene hydroetherification,[19a] hydrotrifluoromethylation,[19b] hydroamination,[19c,d] and hydrohalogenation[19e] reactions. We have also taken advantage of a polar radical crossover cycloaddition mechanism (PRCC) to synthesize tetrahydrofurans arising from the reaction of electron-rich alkenes and allyl alcohols.[19f] This method employed phenylmalononitrile as the redox-active hydrogen atom source to deliver tetrahydrofurans in excellent yields.

Extension of this work to include α,β-unsaturated acids as nucleophiles could provide a direct synthesis of γ-butyrolactones from simple and commercially available starting materials. The attenuated nucleophilicity of α,β-unsaturated acids relative to allyl alcohols was an initial concern; however, we have previously demonstrated success in the anti-Markovnikov hydroacetoxylation of alkenes, where acetic acid was employed as the nucleophile.[19g] We reported that (1) catalytic quantities of base could increase the nucleophilicity of the acid, improving both yield and rate and (2) benzenesulfinic acid, thiophenols, or disulfides could be used in catalytic quantities as viable redox-active cocatalysts.

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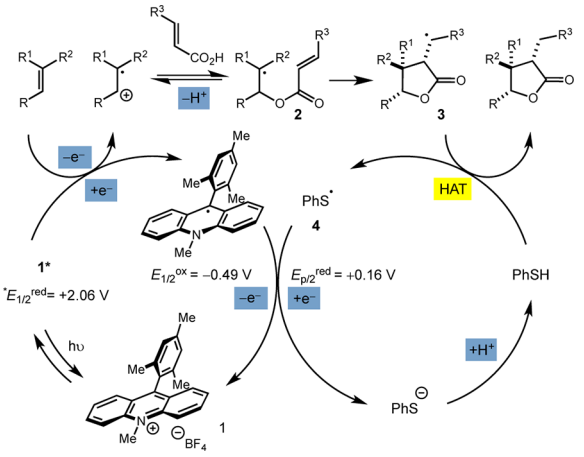
**Scheme 1. Proposed PRCC Mechanism**

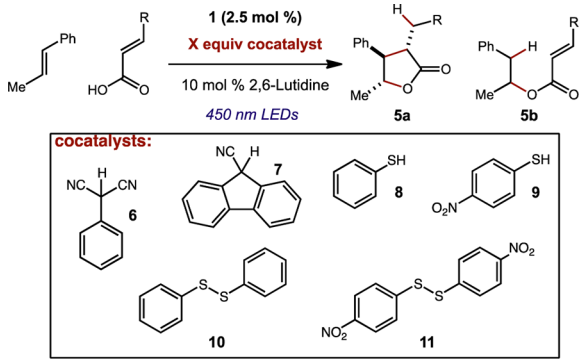



We propose a PRCC mechanism similar to our previous tetrahydrofuran report (Scheme 1). Single electron oxidation of the alkene by the acridinium excited state ($*E_{1/2}^{red}$ = +2.06 V vs SCE) would furnish an electrophilic alkene cation radical. Addition of the carboxylic acid to the alkene cation radical would afford radical **2** poised to undergo a 5-*exo*-*trig* radical cyclization to give **3**. Despite the unusual electronic constraints of this radical cyclization, work by Clive supported the feasibility of this step.[20] Following this, hydrogen atom transfer to carbon-centered radical **3** would furnish the desired $\gamma$-butyrolactone. The success of this proposal was contingent upon the careful selection of an appropriate redox-active hydrogen atom source or surrogate which would meet three criteria: (1) a p$K_a$ high enough to act as a mild conjugate base; (2) a low X–H bond dissociation energy (BDE = 70–80 kcal/mol); and (3) redox activity allowing the resulting radical (**4**) to act as an oxidant to reset the photooxidant.

We began by investigating the reaction between crotonic acid and $\beta$-methylstyrene. Previously developed conditions for the tetrahydrofuran PRCC methodology furnished the desired lactone product **5a** in a 20% yield, with significant amounts of a byproduct (**5b**) resulting from anti-Markovnikov hydroacyloxylation (Table 1, entry 1). Additionally, a Michael addition byproduct between crotonic acid and **6** was observed in small quantities. This prompted us to consider a more sterically hindered H atom donor, such as 9-cyanofluorene (**7**). Unfortunately, **7** also gave modest amounts of lactone product in equal ratio to uncyclized material (entry 2).

We considered that uncyclized byproduct formation was due to the hydrogen atom transfer event occurring prior to the 5-*exo* radical cyclization. When thiophenol (**8**) was employed with crotonic acid, the uncyclized product **5b** dominated (entry 3). Acrylic acid was also found to give **5b** (entry 4). Speculating that the rate of the 5-*exo* radical cyclization might be increased by either stabilizing the forming radical and/or by modulating the polarity of the unsaturated acid, we turned our attention to unsaturated acids bearing radical stabilizing groups. It was found that formation of **5b** could be minimized if a thiol hydrogen atom donor was matched with an unsaturated acid bearing a radical stabilizing group (ester, aryl, silyl, or halogen) at the $\beta$-position.[21] Subjecting mono-*tert*-butyl fumarate to the standard conditions with the inclusion of catalytic amounts of thiophenol produced the lactone adduct in a promising 62% yield (entry 5). The solid, nonvolatile thiol **9** gave the lactone product in similar yields (entry 6). As thiyl radicals are prone to dimerize, we considered

**Table 1. Optimization of Reaction Conditions**[a]




| entry | R | conditions | conversion (%) | yield **5a** (**5b**)[b] (%) |
|---|---|---|---|---|
| 1 | Me | 1 equiv of **6**[c] | 96 | 20 (34) |
| 2 | Me | 1 equiv of **7**[c] | 88 | 18 (20) |
| 3 | Me | 20 mol % of **8** | 63 | 2 (44) |
| 4 | H | 20 mol % of **8** | 50 | 2 (43) |
| 5 | $CO_2t$-Bu | 20 mol % of **8** | 80 | 62 |
| 6 | $CO_2t$-Bu | 20 mol % of **9** | 100 | 64 |
| 7 | *$CO_2t$-Bu* | *10 mol % of **10*** | *99* | *79* |
| 8 | $CO_2t$-Bu | 10 mol % of **11** | 100 | 64 |
| 9 | $CO_2t$-Bu | 10 mol % of **10**, no base | 100 | 64 |

[a]Reactions carried out on a 0.3 mmol scale in $N_2$-sparged $CH_2Cl_2$ [0.15 M] at 23 °C with a 1.1:1 acid/alkene for 24 h unless otherwise noted. [b]Yield of lactone determined by $^1$H NMR analysis of crude reaction. [c]4 days, 5:1 acid/alkene.

that the corresponding disulfides could form and were curious if they would be catalytically active in this context. To test this, we employed disulfides **10** and **11** as potential hydrogen atom surrogates (entries 7 and 8). When **10** was employed in catalytic amounts, the desired adduct was observed in 79% yield (entry 7). As with the previously reported anti-Markovnikov hydroacetoxylation, it was found that catalytic amounts of base could improve reactivity depending on the nucleophilicity of the acid (entry 9).

Having identified the optimal reaction conditions, we turned our attention to the substrate scope, where $\beta$-methylstyrene was investigated in combination with various $\alpha,\beta$-unsaturated acids (Figure 2). Commercially available monoethyl fumarate was a viable substrate for this reaction, giving the expected lactone **12a** in 66% yield (2.2:1 dr); however, mono-*tert*-butyl fumarate was favored due to the simplicity of characterization. The nature of the ester functionality had limited effect on either yield or diastereoselectivity. Cinnamic acid and *p*-chlorocinnamic acid were found to be suitable nucleophiles, producing the desired lactones in 81% (**12c**) and 80% (**12d**) yields, respectively. We were pleased to find that our method was also tolerant to substrates possessing a heteroaromatic group, forging lactone **12e** in moderate yield (44%).

We attempted the use of propiolic acid as the PRCC partner, with the hope of directly forging $\alpha$-methylene-$\gamma$-butyrolactones. Only trace quantities of the desired lactone product were observed. We speculated that the radical cyclization was again the problematic step in this process. However, we were pleased to find that when 3-(trimethylsilyl)propiolic acid was employed as the acid, $\gamma$-butyrolactone **12f** was isolated in excellent yield (85%) as a 1.3:1 mixture of *E*/*Z* isomers. Other alkynoic acids, including 3-phenylpropiolic acid and 3-(thiophene-3-yl)-propiolic acid, could also be employed and afforded the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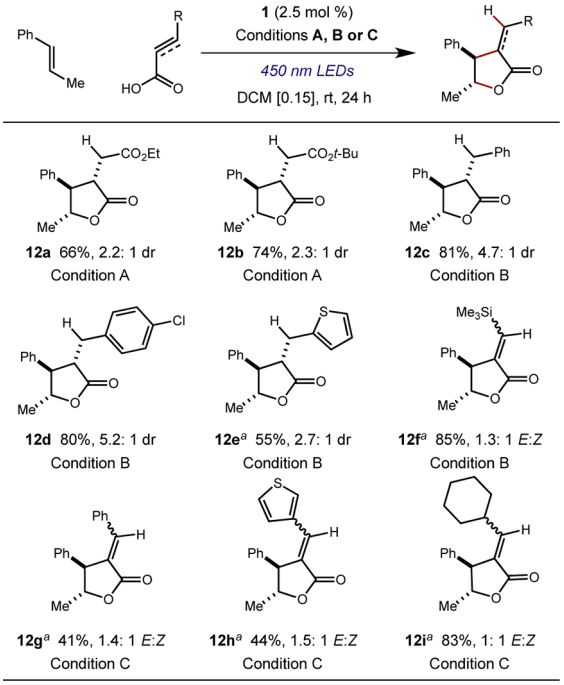



**Figure 2.** Reaction scope of $\alpha,\beta$-unsaturated acids. Reactions carried out in in $N_2$-sparged $CH_2Cl_2$ [0.15 M], average of two isolated yields on 100 mg scale. Conditions A: 1:1.1 alkene/acid, 10 mol % of 2,6-lutidine, 10 mol % of **10**. Conditions B: 3:1 alkene/acid, 15 mol % of **10**. Conditions C: 2−3:1 alkene/acid, 10 mol % of 2,6-lutidine, 15 mol % of **10** carried out for 2−4 days. (a) Reaction carried out for 48 h.

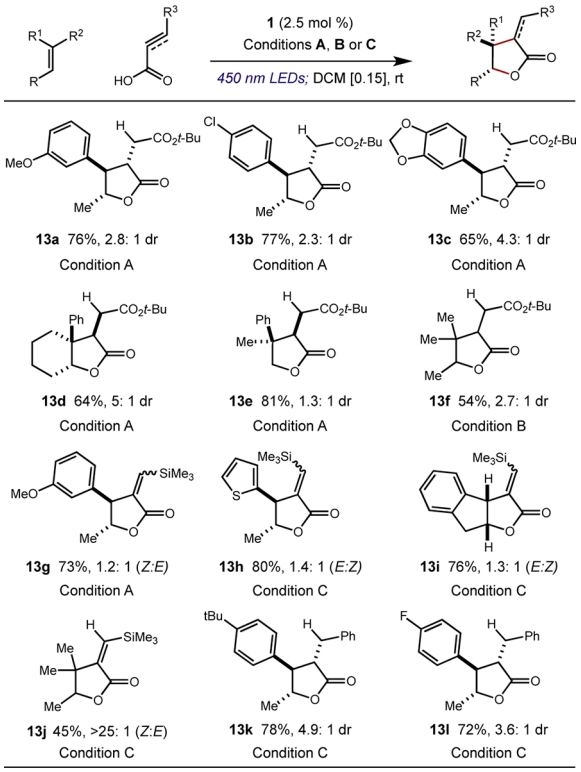
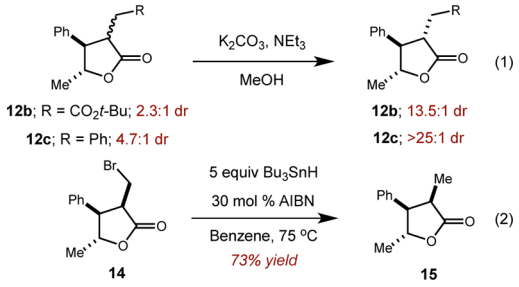



**Figure 3.** Reaction scope of oxidizable alkenes. Reactions carried out in $N_2$-sparged $CH_2Cl_2$ [0.15 M], average of two isolated yields on 100 mg scale. Conditions A: 1:1.1 alkene/acid, 10 mol % of 2,6-lutidine, 10 mol % of **10**. Conditions B: 3:1 alkene/acid, 10 mol % of 2,6-lutidine, 5 mol % of **9**. Conditions C: 3:1 alkene/acid, 15 mol % of **10**

anticipated lactone adducts **12g** and **12h** in 41% and 44% yields, respectively. Neither silyl groups nor aromatic groups at the $\beta$-position are required to stabilize the subsequent radical, as seen by the reaction of 3-cyclohexylpropiolic acid with $\beta$-methylstyrene in an 83% yield (**12i**).

We next tested the scope of oxidizable alkenes in conjunction with either mono-*tert*-butyl fumarate, cinnamic acid, or 3-(trimethylsilyl)propiolic acid for the synthesis of $\gamma$-butyrolactones (Figure 3). Because of the scrambling of alkene geometry through the formation of the radical cation intermediate, oxidizable olefins could be employed as a mixture of $E/Z$ isomers without affecting the high (>20:1) diastereoselectivity with respect to the starting alkene substituents. Mono-*tert*-butyl fumarate, in combination with $\beta$-methylstyrene derivatives of varying electron density, forged the desired lactones (**13a**, **13b**, and **13c**) in good yields. Trisubstituted alkenes such as 1-phenylcyclohexene and 2-methyl-2-butene gave lactones **13d** and **13f** in good yields. $\alpha$-Methylstyrene was a viable substrate, providing the lactone **13e** in 81% yield, albeit with almost no relative stereocontrol (1.3:1 dr). We found that 3-(trimethylsilyl)propiolic acid reacted with a variety of styrene derivatives. Electron-withdrawing $\beta$-methylstyrenes reacted to furnish $\gamma$-butyrolactones (**13g**, **13l**) in 73% and 72% yield, respectively. Moderately electron-donating styrenes were also tolerated, as 4-*tert*-butyl-$\beta$-methylstyrene gave the corresponding lactone in a 78% yield (**13k**). When 3-(trimethylsilyl)propiolic acid was used with 2-methyl-2-butene (**13j**), only the *Z*-isomer was observed. It is possible that the fleeting vinyl radical intermediate equilibrates to relieve nonbonding interactions between the neighboring *gem*-dimethyl group and the bulky trimethylsilyl group.[22]

To upgrade the diasteromeric ratio of the lactone adducts, we submitted lactones **12b** and **12c** to epimerization conditions (eq 1). Not surprisingly, we were able to obtain the thermodynamic isomers in high levels of diastereomeric purity. This epimerization study also confirmed the relative stereochemistry of our major adduct, as the *all-trans* isomer has been noted previously as the most stable conformer.[23]




In an effort to better understand the potential reversibility of the putative radical cyclization step, we synthesized bromide **14** from $\beta$-bromoacrylic acid and $\beta$-methylstyrene using our typical reaction protocol and subjected a single diastereomer of **14** to classical radical hydrodehalogenation conditions (eq 2). If the radical cyclization was reversible, variable quantities of **5b** (R = H) would be expected (Table 1). We observed only clean hydrodebromination of **14** (73% yield) and isolated **15** as a single diastereomer. This result suggests that the radical cyclization step of the PRCC is irreversible and that the predominance of uncyclized adduct, particularly in the reaction of acrylic acid with $\beta$-methylstyrene (Table 1, entry 4), is likely the result of a slow radical cyclization relative to hydrogen atom abstraction.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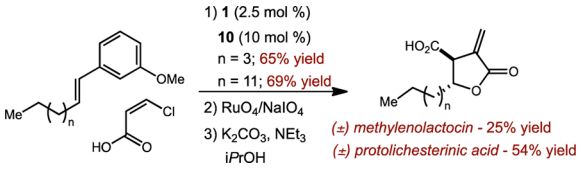
We then elected to apply our new method to the synthesis of two bioactive paraconic acids. Initially we proposed desilylation of a vinyl TMS adduct (e.g., **13g**) and oxidation of an electron-rich aromatic to a carboxylic acid with a $RuO_4/NaIO_4$ system. However, this proved challenging as many conditions used to desilylate the vinyl TMS resulted in unreacted *E*-isomer and alkene isomerization of the desilylated *Z*-isomer. Furthermore, the $RuO_4/NaIO_4$ system reacted preferentially with the $\alpha$-methylene moiety. These issues prompted us to consider $\beta$-haloacrylic acids as reaction partners. Initial results with (*E*)-$\beta$-chloroacrylic acid produced the desired adduct in low yields, where substantial amounts of Michael addition byproduct with thiophenol were obtained. However, the (*Z*)-isomer provided the lactone in good yields and a 1.1:1 dr, while formation of the uncyclized byproduct was suppressed (Scheme 2). Nevertheless, treatment of the chloride isomers with mild basic conditions afforded the desired paraconic acids as single diastereomers.

**Scheme 2. Synthesis of Methylenolactocin and Protolichesterinic Acid**




In summary, our method provides a modular approach to the synthesis of $\gamma$-butyrolactones from a variety of simple, often commercially available, oxidizable olefins and unsaturated acids. Perhaps most importantly, this method could be utilized to rapidly generate libraries of unique $\gamma$-butyrolactone structures for biological testing. A highly diastereoselective synthesis of two important $\alpha$-methylene paraconic acids, methylenolactocin and protolichesterinic acid, was accomplished. Enantioselective variants of this PRCC reaction are the focus of current research efforts.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Author Contributions

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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